

SUBSTITUTE FORM PTO-1390

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
06275-235001

U.S. APPLICATION NO. (If Known, see 37 CFR 1.5)

09/913810

INTERNATIONAL APPLICATION NO.
PCT/GB00/00529INTERNATIONAL FILING DATE
16 February 2000PRIORITY DATE CLAIMED
20 February 1999

TITLE OF INVENTION

DI- AND TRIPEPTIDE NITRILE DERIVATIVES AS INHIBITORS OF CATHEPSIN L AND CATHEPSIN S

APPLICANT(S) FOR DO/EO/US

Howard Tucker, Michael Stewart Large, John Oldfield, Craig Johnstone and Philip Neil Edwards

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern other documents or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

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CERTIFICATE OF MAILING BY EXPRESS MAIL

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I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

Date of Deposit

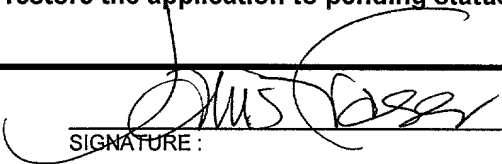
August 17, 01

Signature

Samantha Bell

Typed Name of
Person Signing

Samantha Bell

| | | | | | |
|--|--------------|---|----------------|---|----|
| U.S. APPLICATION NO. (IF KNOWN) 09/913810 | | INTERNATIONAL APPLICATION NO. PCT/GB00/00529 | | ATTORNEY'S DOCKET NUMBER 06275-235001 | |
| 17. <input checked="" type="checkbox"/> The following fees are submitted: Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... \$1000 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100 ENTER APPROPRIATE BASIC FEE AMOUNT = | | | | CALCULATIONS PTO USE ONLY | |
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| Surcharge of \$130 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | | | | \$0.00 | |
| Claims | Number Filed | Number Extra | Rate | | |
| Total Claims | 16 - 20 = | 0 | x \$18 | \$0.00 | |
| Independent Claims | 2 - 3 = | 0 | x \$80 | \$0.00 | |
| MULTIPLE DEPENDENT CLAIMS(S) (if applicable) | | | + \$270 | \$0.00 | |
| TOTAL OF ABOVE CALCULATIONS = | | | | \$860.00 | |
| <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. | | | | \$0.00 | |
| SUBTOTAL = | | | | \$860.00 | |
| Processing fee of \$130 for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)) | | | | \$0.00 | |
| TOTAL NATIONAL FEE = | | | | \$860.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property + | | | | \$0.00 | |
| TOTAL FEES ENCLOSED = | | | | \$860.00 | |
| | | | | Amount to be refunded: | \$ |
| | | | | Charged: | \$ |
| a. <input checked="" type="checkbox"/> A check in the amount of \$860.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. 06-1050 in the amount of \$0.00 to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed. | | | | | |
| NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status. | | | | | |
| SEND ALL CORRESPONDENCE TO: | | | | | |
| Janis K. Fraser, Ph.D., J.D. FISH & RICHARDSON P.C. 225 Franklin Street Boston, Massachusetts 02110-2804 (617) 542-5070 phone (617) 542-8906 facsimile | | | |  SIGNATURE: NAME Janis K. Fraser, Ph.D., J.D. REGISTRATION NUMBER 34,819 | |

09/913810

Attorney's Docket No.: 06275-235001 / FTI/LMS/Z.70485/UST

518 Notarized 17 AUG 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Howard Tucket et al. Art Unit : Unknown
Serial No. : Examiner : Unknown
Filed : Herewith
Title : DI- AND TRIPEPTIDE NITRILE DERIVATIVES AS INHIBITORS OF
CATHEPSIN L AND CATHEPSIN S

Box PCT

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the claims:

Cancel claim 14 without prejudice.

Amend claims 4, 5, 13, and 15-17 as follows:

4. (Amended) A compound as claimed in claim 2, wherein R⁷ is benzyl (optionally substituted with halo (such as chloro)), α -(C₁₋₄ alkyl)-benzyl (optionally substituted with halo (such as chloro)), α,α -di(C₁₋₄ alkyl)-benzyl (optionally substituted with halo (such as chloro)), optionally substituted phenoxyethyl, phenylsulphonylmethyl, benzyloxy, naphthyl or optionally substituted phenyl where said optional substituents are chosen from one or more halo.

CERTIFICATE OF MAILING BY EXPRESS MAIL

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Date of Deposit

August 17 2001

Signature

Samantha Bell
Samantha Bell

Typed or Printed Name of Person Signing Certificate

5. (Amended) A compounds as claimed in claim 2, wherein (AA³) is Leu(S), Phe(S) optionally substituted with C₁₋₆ alkyl or halo and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group or the sulphur moiety in the α -position of the amino acid (AA) may be optionally oxidixed to form an -S(O)₂- or Phe(CH₂S).

13. (Amended) A pharmaceutical composition comprising a compound of formula (I) or Ia), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, and a pharmaceutically acceptable diluent or carrier.

15. (Amended) The use of a compound of formula (I) or (Ia) as claimed in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal.

16. (Amended) The use of a compound of formula (I) or (Ia) as claimed in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal.

17. (Amended) A method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) or (Ia) as claimed in claim 1, or a pharmaceutically acceptable salt thereof.

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REMARKS

Claims 1-13 and 15-17 are pending in this application, claim 14 having been cancelled by the above amendment. Claims 4, 5, 13 and 15-17 are amended to delete multiple dependency. No new matter has been added.

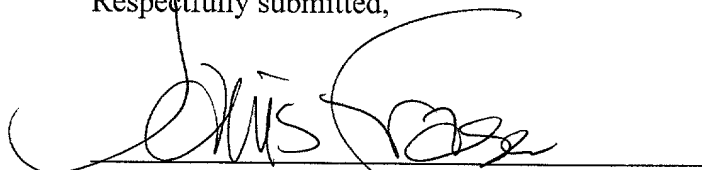
Attached is a marked-up version of the changes being made by the current amendment.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket No. 06275-235001.

Respectfully submitted,

Date:

Aug. 17, 2001



Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

Version with markings to show changes made

In the claims:

Claim 14 has been cancelled.

Claims 4, 5, 13, and 15-17 have been amended as follows:

4. (Amended) A compound as claimed in claim 2 [or 3], wherein R⁷ is benzyl (optionally substituted with halo (such as chloro)), α -(C₁₋₄ alkyl)-benzyl (optionally substituted with halo (such as chloro)), α,α -di(C₁₋₄ alkyl)-benzyl (optionally substituted with halo (such as chloro)), optionally substituted phoxymethyl, phenylsulphonylmethyl, benzyloxy, naphthyl or optionally substituted phenyl where said optional substituents are chosen from one or more halo.

5. (Amended) A compounds as claimed in claim 2, [3 or 4] wherein (AA³) is Leu(S), Phe(S) optionally substituted with [C₁₋₆alkyl] C₁₋₆ alkyl or halo and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group or the sulphur moiety in the α -position of the amino acid (AA) may be optionally oxidised to form an -S(O)₂- or Phe(CH₂S).

13. (Amended) A pharmaceutical composition comprising a compound of formula (I) or Ia), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, [2, 8 or 9] and a pharmaceutically acceptable diluent or carrier.

15. (Amended) The use of a compound of formula (I) or (Ia) as claimed in claim 1, [2, 8 or 9,] or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal.

16. (Amended) The use of a compound of formula (I) or (Ia) as claimed in claim 1, [2, 8 or 9,] or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal.

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17. (Amended) A method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) or (Ia) as claimed in claim 1, [2, 8 or 9,] or a pharmaceutically acceptable salt thereof.

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DI- AND TRIPEPTIDE NITRILE DERIVATIVES AS INHIBITORS OF CATHEPSIN L AND CATHEPSIN S

The present invention relates to compounds that are cysteine protease inhibitors and in particular compounds that are Cathepsin L inhibitors and or Cathepsin S inhibitors especially
5 Cathepsin S inhibitors. The invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents, to pharmaceutical compositions containing them and to a method of treating a Cathepsin L or Cathepsin S mediated disease state.

Cysteine proteases are enzymes important in normal cell physiology, but they are also
10 associated with several disease states including inflammation, metastasis, tissue damage following myocardial infarction, bone resorption and muscle wasting in dystrophic diseases.

Cathepsins B, H, K, L, N and S are cysteinyl proteases involved in normal protein degradation and are normally located in the lysosomes of cells. However, when these enzymes are found outside the lysosomes they have been implicated as playing a causative role in a
15 number of disease states including bone resorption disease such as osteoporosis.

The number of people living to an old age has increased dramatically in recent years. This has been marked by an increase in the number of people having osteoporosis and other diseases associated with old age. Osteoporosis is accompanied by a high incidence of bone fracture resulting in many aged patients being confined to their beds. There is therefore a great
20 need for a pharmaceutical composition to treat or prevent this disease.

Living bone is continuously being remodelled and replenished by the process of resorption and deposition of the protein matrix and calcium minerals. These events are facilitated by the osteoclast, which has the ability to degrade and demineralise the bone, and the osteoblast which is responsible for new bone generation. In normal situations these
25 processes are intimately linked resulting in little alteration of bone mass. However, pathological conditions exist in which there is an imbalance between their activities resulting in increased degradation and demineralisation of bone and the development of fragile and/or brittle bone structure, as seen during osteoporosis. While the exact mechanism for this resorption is not known, increased osteoclast activity, as realised by increased proteolytic
30 activity, is a contributing factor, and selective inhibition of proteolytic action may result in the arrest or reversal of bone loss. The lysosomal cysteine proteinases, Cathepsins B, H, K, L, N

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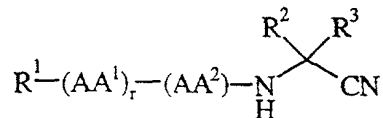
and S have been postulated as the proteinases that are responsible for osteoclast bone resorption, because of their ability to degrade insoluble type I collagens at low pH.

Cathepsins B, H, K, L, N and S have been further implicated as playing a causative role in other diseases such as rheumatoid arthritis, osteoarthritis, tumour metastasis, pneumocystitis, *Crithidia fusiculata*, malaria, *trypanosoma brucei brucei*, schistosomiasis, periodontal disease, metachromatic leukodystrophy and muscular dystrophy. Cathepsins B, H, K, L, N and S, either alone or together, have also been implicated as playing a causative role in chronic obstructive pulmonary disease (COPD).

In recent years a number of synthetic inhibitors of cysteine proteases have been disclosed. US 5,055,451 discloses a series of peptidyl methyl ketones as thiol protease inhibitors; WO 95/15749 discloses peptidyl ketones with heterocyclic leaving groups as cysteine protease inhibitors; the *in vivo* inhibition of Cathepsin B by peptidyl (acyloxy) methyl ketones was discussed in *J. Med. Chem.* **1994**, 37, 1833-40 and these types of compounds as inhibitors of cysteine protease inhibitors were also discussed in *J. Am. Chem. Soc.*, **1988**, 110, 4429-4431; peptidyl diazomethyl ketones as specific inactivators of thiol proteinases was discussed in *J. Biol. Chem.*, **1981**, 256, 4, 1923-8 and in *Methods in Enzymology*, **1981**, 80, 820-5; the inhibiting activities of 1-peptidyl-2-haloacetyl hydrazines towards Cathepsin B and calpains was discussed in *Eur. J. Med. Chem.*, **1993**, 28 297-311 and peptidyl fluoromethyl ketones as inhibitors of Cathepsin B and the implication for treatment of Rheumatoid arthritis was discussed in *Biochemical Pharmacology*, **1992**, 44, 6, 1201-7. Thus, there is a great need for a specific cysteine protease inhibitor, especially a Cathepsin L inhibitor or a Cathepsin S inhibitor.

The present invention discloses compounds with inhibitory activity of cysteine proteases and in particular of Cathepsin L and or Cathepsin S. The compounds of the invention are also useful in the treatment of chronic obstructive pulmonary disease (COPD).

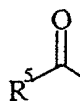
Accordingly the present invention provides a compound of formula (I):



(I)

wherein *r* is 0 or 1;

- R^1 is hydrogen, optionally substituted benzyl where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl, or R^1 is a group of formula (II):



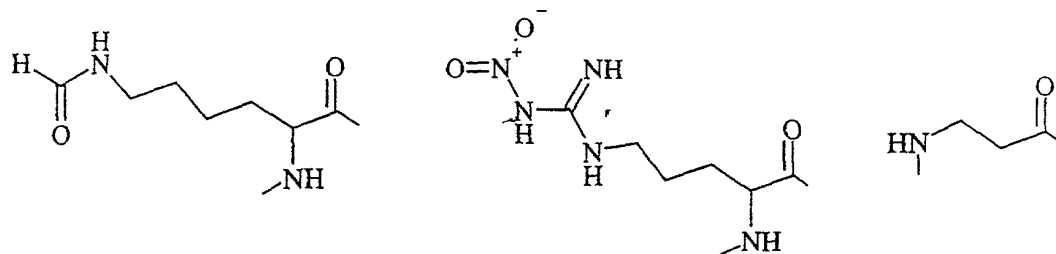
(II)

- wherein R^5 is C_{1-6} alkyl (optionally substituted with an optionally substituted phenyl, an optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted phenoxy, optionally substituted phenylsulphonyl, optionally substituted C_{3-12} cycloalkyl or Het), C_{1-6} alkoxy, optionally substituted phenyl, optionally substituted naphthyl, optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted C_{3-12} cycloalkyl, Het or optionally substituted phenyl C_{1-6} alkoxy; where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;
- R^2 is H, C_{1-6} alkyl [optionally substituted with one or more of hydroxy, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, R^4 , R^4C_{1-6} alkylsulphanyl, R^4C_{1-6} alkylsulphinyl, R^4C_{1-6} alkylsulphonyl], or R^2 is C_{1-6} alkoxy [optionally substituted with one or more of C_{2-6} alkenyl, C_{2-6} alkynyl, R^4 , R^4C_{2-6} alkenyl, R^4C_{2-6} alkynyl, Het and trifluoromethyl], or R^2 is C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, R^4 , R^4S , R^4C_{1-6} alkylsulphanyl, N -(R^4C_{1-6} alkyl)carbamoyl, N -(Het C_{1-6} alkyl)carbamoyl, C_{1-6} alkanoylamino, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl or C_{1-6} alkylsulphonyl; R^4 is an optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms, said optional

- substituents being chosen from one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl;

R³ is H or C₁₋₆alkyl;

(AA¹) and (AA²) are independently chosen from Ala, Arg, Cys, Gly, His, Ile, Leu, Lys, Met, Phe, Ser, Thr, Trp, Tyr, Val,

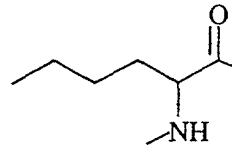
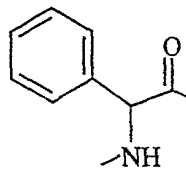
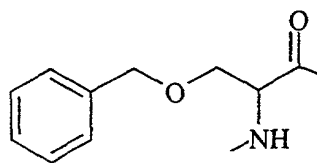


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Lys(CHO),

Arg(NO₂),

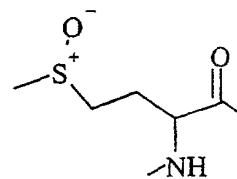
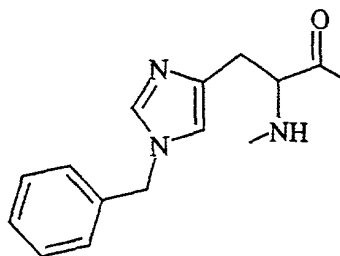
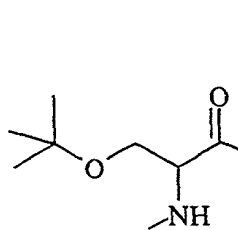
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Ser(Bzl),

Ph-Gly,

Nle,



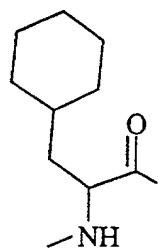
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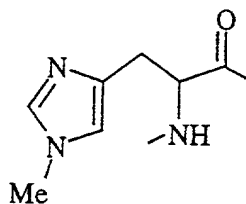
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Met(O),

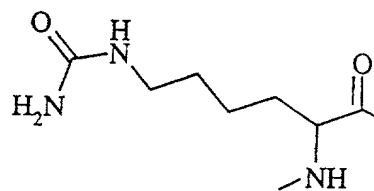
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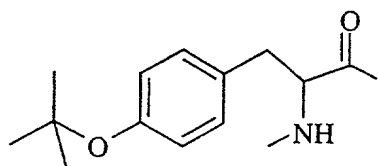
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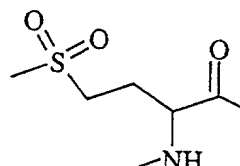
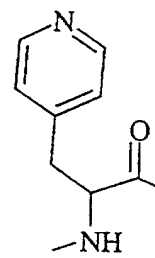
His(Me),



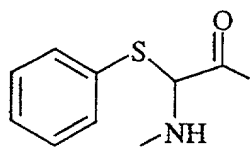
Cit,



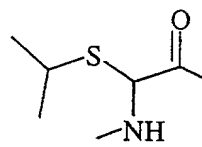
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Met(O₂),

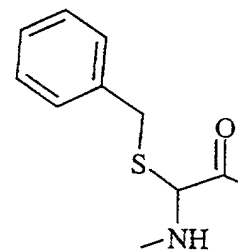
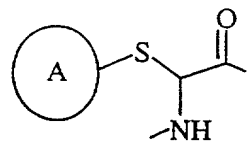
Pyr-Ala



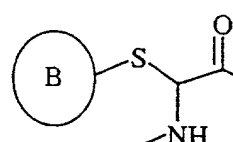
Phe(S),



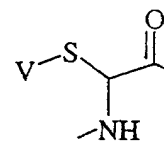
Leu(S),

Phe(CH₂S),

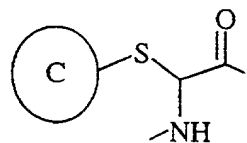
Cy(S)-Gly,



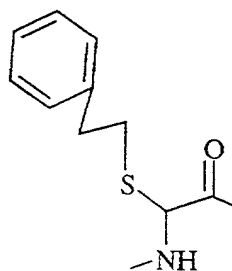
Hetar(S)-Gly,



alk(S)-Gly or



Het(S)-Gly, and

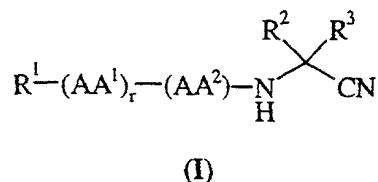
Phe(CH₂CH₂)S;

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20000701854660

wherein Ring A is C₃₋₁₂cycloalkyl; Ring B is a 5 or 6 membered heteroaryl ring; Ring C is Het; V is C₁₋₆alkyl excluding isopropyl; the nitrogen of the amino acid may optionally be alkylated with C₁₋₆alkyl; the phenyl group of Phe(S) and Rings A and B are optionally substituted with one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl or *N,N*-(C₁₋₆alkyl)₂sulphamoyl; the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group; the sulphur moiety in the α -position of the amino acid (AA³) may be optionally oxidised to form an -S(O)₂- or -S(O)- moiety; and Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; or a pharmaceutically acceptable salt thereof.

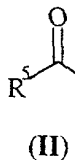
In one aspect the present invention provides a compound of formula (I):



wherein:

r is 0 or 1;

R¹ is optionally substituted benzyl where said optional substituents are chosen from one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl or **R**¹ is a group of formula (II):

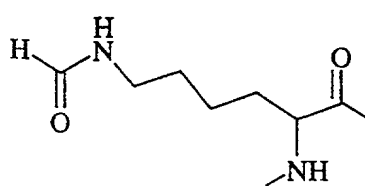


wherein R^5 is C_{1-6} alkyl (optionally substituted with an optionally substituted phenyl, an optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted phenoxy, optionally substituted phenylsulphonyl, optionally substituted C_{3-12} cycloalkyl or Het), C_{1-6} alkoxy, optionally substituted phenyl, optionally substituted naphthyl, optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted C_{3-12} cycloalkyl, Het, optionally substituted phenyl C_{1-6} alkoxy where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

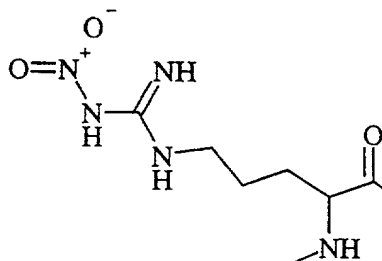
R^2 is an optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

R^3 is H; and

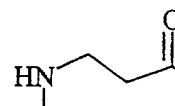
(AA^1) and (AA^2) are independently chosen from Ala, Arg, Cys, Gly, His, Ile, Leu, Lys, Met, Phe, Ser, Thr, Trp, Tyr, Val,



Lys(CHO),

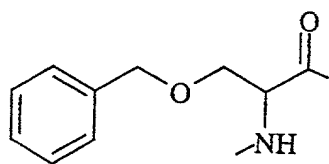


Arg(NO₂),

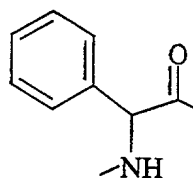


β -Ala,

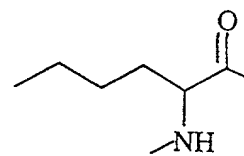
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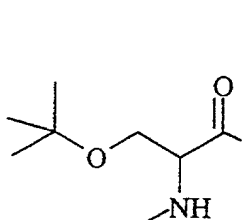
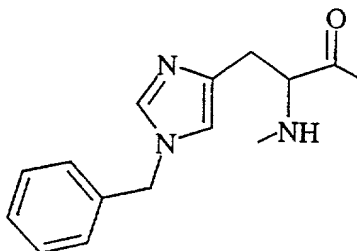
Ser(Bzl),



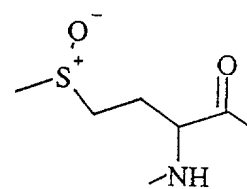
Ph-Gly,



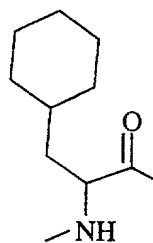
Nle,

Ser(O^tBu),

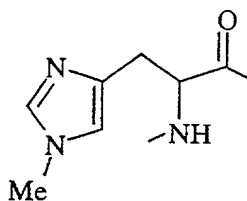
His(Bzl),



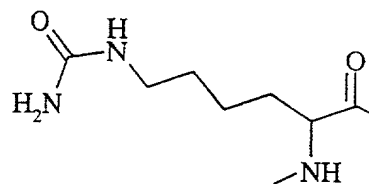
Met(O),



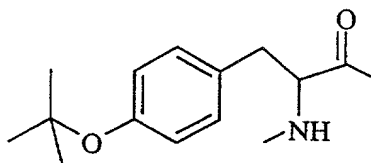
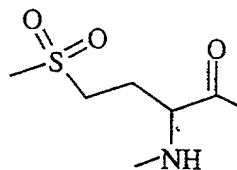
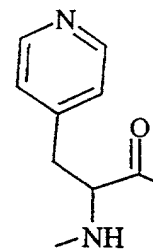
Cha,



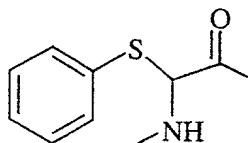
His(Me),



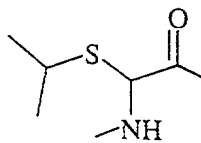
Cit,

Tyr(^tBu),Met(O₂),

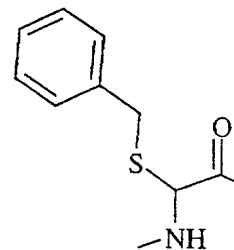
Pyr-Ala



Phe(S),

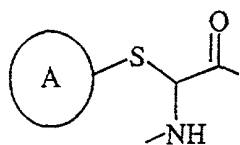


Leu(S),

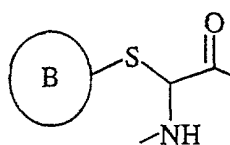
Phe(CH₂S),

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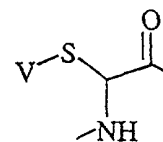
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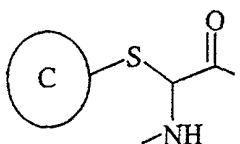
Cy(S)-Gly,



Hetar(S)-Gly,



alk(S)-Gly or



Het(S)-Gly;

- 5 wherein Ring A is C_{3-12} cycloalkyl, Ring B is a 5 or 6 membered heteroaryl ring, Ring C is Het, V is C_{1-6} alkyl excluding isopropyl, the nitrogen of the amino acid may optionally be alkylated with C_{1-6} alkyl and the phenyl group of Phe(S) and Rings A and B may be optionally substituted with one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino,
- 10 N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl or the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group;
- 15 or a pharmaceutically acceptable salt thereof.

- In this specification the term 'alkyl' includes straight chained and branched structures and ring systems. For example, C_{1-6} alkyl includes propyl, isopropyl, *t*-butyl, cyclopropyl and cyclohexyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only, references to individual branched chain alkyl groups such as
- 20 'isopropyl' are specific for the branched chain version only and references to individual cycloalkyl groups such as cyclohexyl are specific to the cyclic groups only.

A similar convention applies to other radicals, for example "hydroxy C_{1-6} alkyl" includes 1-hydroxyethyl and 2-hydroxyethyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

- 25 "Het" means, unless otherwise further specified, a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms. Preferably these ring heteroatoms

are selected from nitrogen, oxygen and sulphur. Examples of "Het" include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl.

Unless otherwise defined standard amino acid abbreviations are used. For example "Ala" refers to alanine and "Gly" refers to glycine.

- 5 "5- or 6- membered heteroaryl ring" means, unless otherwise further specified, a 5- or 6- membered ring that contains some degree of unsaturation, with up to four ring heteroatoms selected from nitrogen, oxygen and sulphur. Examples of "5- or 6- membered heteroaryl ring" include thienyl, furyl, imidazolyl, thiazolyl, pyrimidinyl, pyridinyl, pyrrolyl and pyrazolyl. Examples of "6 membered heteroaryl ring" include pyrimidinyl, pyridinyl, pyrazinyl and
10 pyridazinyl. Examples of "5 membered heteroaryl ring" include thienyl, furyl, imidazolyl, thiazolyl, pyrrolyl and oxadiazolyl.

- Examples of "C₁₋₆alkanoyloxy" are acetoxo and propionyloxy. Examples of "C₁₋₆alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C₁₋₆alkoxy" include methoxy, ethoxy and propoxy. Examples of
15 "C₁₋₆alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C₁₋₆alkylsulphanyl" include methylthio and ethylthio. Examples of "C₁₋₆alkylsulphinyl" include methylsulphinyl and ethylsulphinyl. Examples of "C₁₋₆alkylsulphonyl" include mesyl and ethylsulphonyl. Examples of "C₁₋₆alkanoyl" include acetyl and propionyl. Examples of "C₁₋₆alkylamino" include methylamino and ethylamino. Examples of "*N,N*-(C₁₋₆alkyl)₂amino" include *N,N*-dimethylamino, *N,N*-diethylamino and *N*-ethyl-*N*-methylamino. Examples of
20 "*N*-(C₁₋₆alkyl)carbamoylC₁₋₆alkyl" are 2-(methylamino)carbonylethyl and 3-(ethylamino)carbonylpropyl. Examples of "*N,N*-(C₁₋₆alkyl)₂carbamoylC₁₋₆alkyl" are 2-(dimethylamino)carbonylethyl and 3-(*N*-methyl-*N*-ethylamino)carbonylpropyl. Examples of "C₂₋₆alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C₂₋₆alkynyl" are ethynyl,
25 1-propynyl and 2-propynyl. Examples of "*N*-(C₁₋₆alkyl)carbamoyl" are *N*-methylaminocarbonyl and *N*-ethylaminocarbonyl. Examples of "*N,N*-(C₁₋₆alkyl)₂carbamoyl" are *N,N*-dimethylaminocarbonyl and *N*-methyl-*N*-ethylaminocarbonyl. Examples of "*N*-(C₁₋₆alkyl)sulphamoyl" are *N*-methylsulphamoyl and *N*-ethylsulphamoyl. Examples of "*N,N*-(C₁₋₆alkyl)₂sulphamoyl" are *N,N*-dimethylsulphamoyl and *N,N*-diethylsulphamoyl. Examples of "*R*⁴C₁₋₆alkylsulphanyl" include *R*⁴methylthio and 2-*R*⁴ethylthio. Examples of "*R*⁴C₁₋₆alkylsulphinyl" include *R*⁴methylsulphinyl and 2-*R*⁴ethylsulphinyl. Examples of "*R*⁴C₁₋₆alkylsulphonyl" include *R*⁴mesyl and 2-

R^4 ethylsulphonyl. Examples of R^4C_{2-6} alkenyl are 2- R^4 vinyl and 3- R^4 allyl. Examples of “ R^4C_{2-6} alkynyl” are 2- R^4 ethynyl and 3- R^4 propyn-1-yl. Examples of “ $N-(R^4C_{1-6}$ alkyl)carbamoyl” are R^4 methylaminocarbonyl and 2- R^4 ethylaminocarbonyl. Examples of “ $N-(HetC_{1-6}$ alkyl)carbamoyl” are morpholinomethylaminocarbonyl and 2-(piperidinoethyl)aminocarbonyl. Examples of “ C_{3-12} cycloalkyl” are cyclopropyl, cyclopentyl and cyclohexyl.

Where optional substituents are chosen from “one or more” groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. For example where optional substituents are chosen from one or more halo, C_{1-6} alkoxy and C_{1-6} alkyl, examples of possible combinations of substituents include 1) a bromo group, 2) two chloro groups, 3) a methoxy, ethoxy and propoxy substituent, 4) a fluoro and a methoxy group, 5) a methoxy, a methyl and an ethyl group, and 6) a chloro, a methoxy and an ethyl group.

According to a further feature of the invention there is provided a compound of formula (I) wherein:

r is 0 or 1;

R^1 is optionally substituted benzyl where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, $N,N-(C_{1-6}alkyl)_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, $N-(C_{1-6}alkyl)carbamoyl$, $N,N-(C_{1-6}alkyl)_2carbamoyl$, $C_{1-6}alkoxycarbonyl$, mercapto, $C_{1-6}alkylsulphanyl$, $C_{1-6}alkylsulphinyl$, $C_{1-6}alkylsulphonyl$, sulphamoyl, $N-(C_{1-6}alkyl)sulphamoyl$ and $N,N-(C_{1-6}alkyl)_2sulphamoyl$ or R^1 is a group of formula (II) wherein R^5 is C_{1-6} alkyl (optionally substituted with an optionally substituted phenyl, an optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted phenoxy or optionally substituted phenylsulphonyl), C_{1-6} alkoxy, optionally substituted phenyl, optionally substituted naphthyl, optionally substituted phenyl C_{1-6} alkoxy where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, $N,N-(C_{1-6}alkyl)_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, $N-(C_{1-6}alkyl)carbamoyl$, $N,N-(C_{1-6}alkyl)_2carbamoyl$, $C_{1-6}alkoxycarbonyl$, mercapto, $C_{1-6}alkylsulphanyl$,

C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl;

- R²** is H, C₁₋₆alkyl [optionally substituted with one or more of hydroxy, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, R⁴, R⁴C₁₋₆alkylsulphanyl, R⁴C₁₋₆alkylsulphinyl, R⁴C₁₋₆alkylsulphonyl], or **R²** is C₁₋₆alkoxy [optionally substituted with one or more of C₂₋₆alkenyl, C₂₋₆alkynyl, R⁴, R⁴C₂₋₆alkenyl, R⁴C₂₋₆alkynyl, Het and trifluoromethyl], or **R²** is C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, R⁴, R⁴S, R⁴C₁₋₆alkylsulphanyl, *N*-(R⁴C₁₋₆alkyl)carbamoyl, *N*-(HetC₁₋₆alkyl)carbamoyl, C₁₋₆alkanoylamino, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl wherein **R⁴** is an optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl;

R³ is H or C₁₋₆alkyl; and

- (AA¹) and (AA²) are independently chosen from Ala, Arg, Cys, Gly, His, Ile, Leu, Lys, Met, Phe, Ser, Thr, Trp, Tyr, Val, Lys(CHO), Arg(NO₂), β-Ala, Ser(Bzl), Ph-Gly, Nle, Ser(O^tBu), His(Bzl), Met(O), Cha, His(Me), Cit, Tyr(^tBu), Met(O₂), Pyr-Ala, Phe(S), Leu(S) or Phe(CH₂S); wherein the nitrogen of the amino acid may optionally be alkylated with C₁₋₆alkyl and the phenyl group of Phe(S) may be optionally substituted with one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl or the phenyl group may be fused to another phenyl group to form a naphthyl group;
- or a pharmaceutically acceptable salt thereof.

Preferred values for R¹, r, AA¹, AA², R² and R³ are as follows.

- In one aspect of the invention preferably R^1 is optionally substituted benzyl where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl,
- 5 N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl or R^1 is a group of formula (II) wherein R^5 is C_{1-6} alkoxy, optionally substituted C_{3-12} cycloalkyl or optionally substituted phenyl C_{1-6} alkoxy where said optional substituents are chosen from one or more of C_{1-6} alkyl,
- 10 halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl.
- 15 Preferably R^1 is benzyl or a group of formula (II) wherein R^5 is C_{1-6} alkyl (optionally substituted with a 6 membered heteroaryl ring, phenyl, phenylsulphonyl or phenoxy optionally substituted with one or more halo), C_{1-6} alkoxy, phenyl (optionally substituted with one or more halo), naphthyl and phenyl C_{1-6} alkoxy.
- In another aspect of the invention preferably R^1 is benzyl or a group of formula (II) wherein R^5 is C_{1-6} alkyl (optionally substituted with a 6 membered heteroaryl ring, phenyl, phenylsulphonyl, C_{3-12} cycloalkyl or phenoxy optionally substituted with one or more halo), C_{1-6} alkoxy, phenyl (optionally substituted with one or more halo), naphthyl, C_{3-12} cycloalkyl, Het, and phenyl C_{1-6} alkoxy.
- 20 More preferably R^1 is benzyl or a group of formula (II) wherein R^5 is methyl, methoxy, ethoxy, propoxy, 'butoxy, phenyl, 2,4-dichlorophenyl, naphthyl, benzyloxy, pyridylmethyl, benzyl, 2,4,6-trichlorophenoxymethyl and phenylsulphonylmethyl.
- In another aspect of the invention more preferably R^1 is benzyl or a group of formula (II) wherein R^5 is methyl, methoxy, ethoxy, propoxy, 'butoxy, phenyl, 2,4-dichlorophenyl, naphthyl, benzyloxy, pyridylmethyl, benzyl, 2,4,6-trichlorophenoxymethyl,
- 30 phenylsulphonylmethyl, morpholino, cyclohexyl, cyclopentyl, cyclohexylmethyl and piperidino.

Particularly R^1 is a group of formula (II) wherein R^5 is methyl, ^tbutoxy, benzyloxy and pyridylmethyl.

In another aspect of the invention particularly R^1 is a group of formula (II) wherein R^5 is methyl, ^tbutoxy, benzyloxy, pyridylmethyl, morpholino, cyclohexyl, cyclopentyl,
5 cyclohexylmethyl and piperidino.

More particularly R^1 is a group of formula (II) wherein R^5 is methyl, ^tbutoxy, benzyloxy and 4-pyridylmethyl.

In another aspect of the invention particularly R^1 is a group of formula (II) wherein R^5 is morpholino, cyclohexyl, cyclopentyl, cyclohexylmethyl and piperidino.

10 In one aspect of the invention preferably r is 0.

In another aspect of the invention preferably r is 1.

Preferably AA^1 is Leu, Pyr-Ala and Phe wherein the nitrogen of the amino acid is optionally substituted with C_{1-6} alkyl.

More preferably AA^1 is Leu and the nitrogen of the amino acid is unsubstituted.

15 Preferably AA^2 is Phe, Leu, Ile, Tyr, Tyr(^tBu), Val, Cha, Leu(S), Phe(S) and Phe(CH_2S) and the nitrogen of the amino acid is unsubstituted and the phenyl group of Phe(S) is optionally substituted with halo, C_{1-6} alkyl or is fused to another phenyl group to form a naphthyl group.

20 More preferably AA^2 is Tyr, Leu and Phe and the nitrogen of the amino acid is unsubstituted.

Preferred combinations of r , AA^1 and AA^2 are as follows.

When $r = 0$ preferably AA^2 is Phe, Leu, Ile, Val, Tyr, Tyr(^tBu), Leu(S), Phe(S) and Phe(CH_2S) and the nitrogen of the amino acid is unsubstituted and the phenyl group of Phe(S) is optionally substituted with halo, C_{1-6} alkyl or is fused to another phenyl group to form a
25 naphthyl group.

When $r = 0$ more preferably AA^2 is Tyr.

When $r = 1$ preferably AA^1-AA^2 is Leu-Leu, Pyr-Ala-Leu, Phe-Leu, Leu-Phe, Leu-Ile, Leu-Val, Leu-Cha and (N-Me)Leu-Leu.

When $r = 1$ more preferably AA^1-AA^2 is Leu-Leu and Leu-Phe.

30 In another aspect of the invention preferably (AA^1) and (AA^2) are both independently selected from Phe(S), Leu(S), Phe(CH_2S), Cy(S)-Gly, Hetar(S)-Gly, alk(S)-Gly and Het(S)-Gly wherein Phe(S) and Rings A and B may be optionally substituted as hereinbefore defined

and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group.

In a further aspect of the invention preferably r is 0 and (AA²) is selected from Phe(S), Leu(S), Phe(CH₂S), Cy(S)-Gly, Hetar(S)-Gly, alk(S)-Gly and Het(S)-Gly wherein Phe(S) and
5 Rings A and B may be optionally substituted as hereinbefore defined and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group.

In a further aspect of the invention preferably r is 0 and (AA²) is selected from Phe(S), Leu(S) and Phe(CH₂S) wherein Phe(S) may be optionally substituted as hereinbefore defined and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a
10 naphthyl group.

In one aspect of the invention preferably R² is C₁₋₆alkoxy [optionally substituted with one or more of C₂₋₆alkenyl, C₂₋₆alkynyl, R⁴, R⁴C₂₋₆alkenyl, R⁴C₂₋₆alkynyl, Het and trifluoromethyl], or R² is C₂₋₆alkenyl, C₂₋₆alkynyl, carbamoyl, R⁴, R⁴S, R⁴C₁₋₆alkylsulphanyl, C₁₋₆alkanoylamino, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphonyl wherein R⁴ is
15 an optionally substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl,
20 *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl.

Preferably R² is hydrogen, C₁₋₆alkyl [optionally substituted with C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphonyl or R⁴], C₁₋₆alkoxy [optionally substituted with C₂₋₆alkynyl] and R⁴-
25 wherein R⁴ is an optionally substituted phenyl or an optionally substituted 5 membered heteroaryl ring containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C₁₋₆alkyl and halo.

More preferably R² is hydrogen, methyl, ethyl, propyl, isobutyl, furyl, thienyl, pyrazolyl (optionally substituted with one or more of methyl and bromo), imidazolyl, 1,2,4-triazolyl, phenyl, benzyl, 2-methylthioethyl, methylthio, ethylthio, isopropylthio, mesylethyl,
30 methoxy, ethoxy, isopropoxy and 2-propynyloxy.

Particularly R^2 is furyl, pyrazolyl (optionally substituted with one or more of methyl and bromo), imidazolyl, 1,2,4-triazolyl, benzyl, 2-methylthioethyl, isopropylthio, methoxy, isopropoxy and 2-propynyloxy.

More particularly R^2 is fur-2-yl, pyrazol-1-yl, 3,5-dimethylpyrazol-1-yl, 4-bromo-3,5-dimethylpyrazol-1-yl, imidazol-1-yl, 1,2,4-triazol-1-yl, benzyl, methylthioethyl, isopropylthio, methoxy, isopropoxy and 2-propynyloxy.

In another aspect of the invention preferably R^2 is an optionally substituted 5 membered heteroaryl ring containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl.

More preferably R^2 is thienyl, furyl and pyrazolyl.

Particularly R^2 is thienyl.

Preferably R^3 is hydrogen.

According to one aspect of the present invention there is provided a compound of the formula (I) wherein:

R^1 is a group of formula (II) wherein R^5 is morpholino, cyclohexyl, cyclopentyl, cyclohexylmethyl and piperidino;

r is 0 or 1;

(AA^1) and (AA^2) are both independently selected from Phe(S), Leu(S), Phe(CH_2S), Cy(S)-Gly, Heta(S)-Gly, alk(S)-Gly and Het(S)-Gly wherein Phe(S) and Rings A and B may be optionally substituted as hereinbefore defined and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group;

R^2 is an optionally substituted 5 membered heteroaryl ring containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkoxycarbonyl, mercapto,

C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, N-(C₁₋₆alkyl)sulphamoyl and N,N-(C₁₋₆alkyl)₂sulphamoyl; and

R³ is hydrogen;

or a pharmaceutically acceptable salt thereof.

5 According to another aspect of the present invention there is provided a compound of the formula (I) wherein:

R¹ is benzyl or a group of formula (II) wherein R⁵ is C₁₋₆alkyl (optionally substituted with a 6 membered heteroaryl ring, phenyl, phenylsulphonyl or phenoxy optionally substituted with one or more halo), C₁₋₆alkoxy, phenyl (optionally substituted with one or more halo),
10 naphthyl or phenylC₁₋₆alkoxy;

r is 0 or 1;

AA¹ is Leu, Pyr-Ala or Phe wherein the nitrogen of the amino acid is optionally substituted with C₁₋₆alkyl;

AA² is Phe, Leu, Ile, Tyr, Tyr(^tBu), Val, Cha, Leu(S), Phe(S) and Phe(CH₂S) and the
15 nitrogen of the amino acid is unsubstituted and the phenyl group of Phe(S) is optionally substituted with halo, C₁₋₆alkyl or is fused to another phenyl group to form a naphthyl group;

R² is hydrogen, C₁₋₆alkyl [optionally substituted with C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphonyl or R⁴], C₁₋₆alkoxy [optionally substituted with C₂₋₆alkynyl,] or R⁴ - wherein R⁴ is an optionally substituted phenyl or an optionally substituted 5 membered heteroaryl ring
20 containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C₁₋₆alkyl or halo; and

R³ is hydrogen;

or a pharmaceutically acceptable salt thereof.

A further preferred class of compounds is that of formula (I) wherein:

25 R¹ is a group of formula (II) wherein R⁵ is methyl, ^tbutoxy, benzyloxy or pyridylmethyl;

r is 0 or 1;

AA¹ is Leu wherein the nitrogen of the amino acid is unsubstituted;

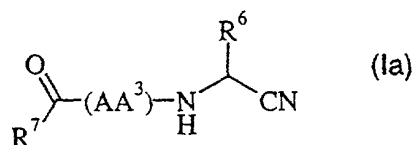
AA² is Tyr, Leu or Phe wherein the nitrogen of the amino acid is unsubstituted;

30 R² is furyl, pyrazolyl (optionally substituted with one or more methyl or bromo), imidazolyl, 1,2,4-triazolyl, benzyl, methylthioethyl, isopropylthio, methoxy, isopropoxy or propynyloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt thereof.

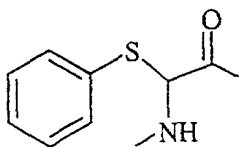
In yet another aspect the present invention provides a compound of formula (Ia):



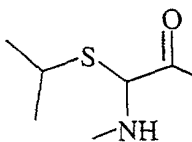
5 wherein:

- R^7 is optionally substituted benzyl, optionally substituted phenoxymethyl, optionally substituted phenylsulphonylmethyl, optionally substituted benzyloxy, optionally substituted naphthyl, optionally substituted phenyl or t-butoxy where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano,
- 10 C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;
- 15 R^6 is hydrogen, optionally substituted phenyl or optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms; said optional substituents being chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl,
- 20 N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

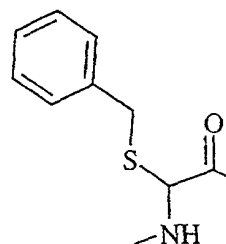
(AA^3) is selected from:



Phe(S),

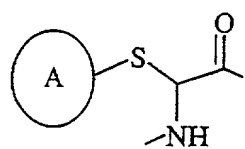


Leu(S),

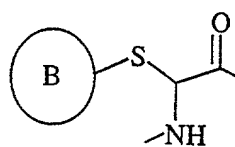


Phe(CH₂S),

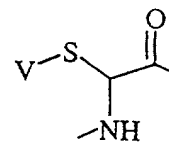
19



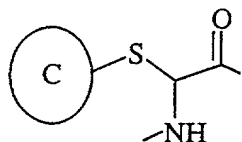
Cy(S)-Gly,



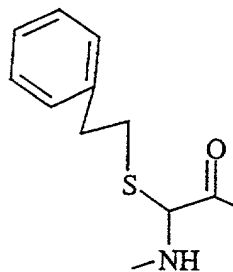
Hetar(S)-Gly,



alk(S)-Gly,

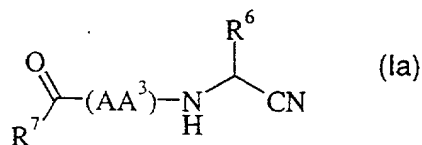


Het(S)-Gly, and

Phe(CH₂CH₂)S;

- 5 wherein Ring A is C₃₋₁₂cycloalkyl, Ring B is a 5 or 6 membered heteroaryl ring, Ring C is Het, V is C₁₋₆alkyl excluding isopropyl; the nitrogen of the amino acid may optionally be alkylated with C₁₋₆alkyl; the phenyl group of Phe(S) and Rings A and B may be optionally substituted with one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino,
- 10 *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl; the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group; and the sulphur moiety in the
- 15 α-position of the amino acid (AA) may be optionally oxidised to form an -S(O)₂- or -S(O)- moiety; and
- Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms;
- or a pharmaceutically acceptable salt thereof.

- 20 In a still further aspect the present invention provides a compound of formula (Ia):



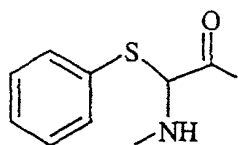
wherein:

R^7 is optionally substituted benzyl, optionally substituted phenoxymethyl, optionally substituted phenylsulphonylmethyl, optionally substituted benzyloxy, optionally substituted naphthyl, optionally substituted phenyl or t-butoxy where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano,

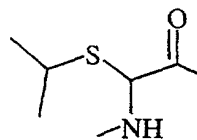
- 5 C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

- 10 R^6 is hydrogen or an optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms said optional substituents being chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, 15 N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

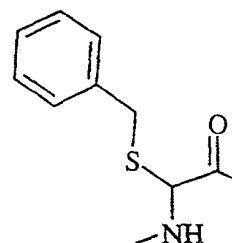
(AA^3) is selected from:



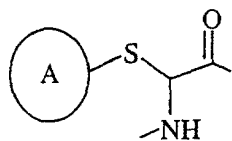
Phe(S),



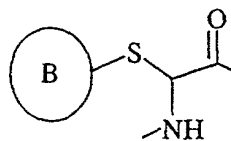
Leu(S),



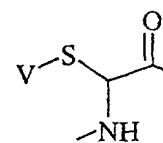
Phe(CH_2S),



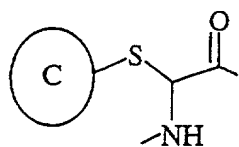
Cy(S)-Gly,



Hetar(S)-Gly,



alk(S)-Gly and



Het(S)-Gly;

wherein Ring A is C₃₋₁₂cycloalkyl, Ring B is a 5 or 6 membered heteroaryl ring, Ring C is
 Het, V is C₁₋₆alkyl excluding isopropyl, the nitrogen of the amino acid may optionally be
 5 alkylated with C₁₋₆alkyl and the phenyl group of Phe(S) and Rings A and B may be optionally
 substituted with one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy,
 cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino,
 N,N-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl,
 N-(C₁₋₆alkyl)carbamoyl, N,N-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto,
 10 C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl,
 N-(C₁₋₆alkyl)sulphamoyl and N,N-(C₁₋₆alkyl)₂sulphamoyl, the phenyl group of Phe(S) may be
 fused to another phenyl group to form a naphthyl group and the sulphur moiety in the
 α-position of the amino acid (AA) may be optionally oxidised to form an -S(O)₂- or -S(O)-
 moiety; or a pharmaceutically acceptable salt thereof. The variable Het is a fully saturated
 15 monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms.

Preferred values for R⁷, AA³ and R⁶ for the compound of formula (Ia) are as follows.

The variable R⁷ is, for example, benzyl (optionally substituted with halo (such as
 chloro)), α-(C₁₋₄ alkyl)-benzyl (optionally substituted with halo (such as chloro)), α,α-di(C₁₋₄
 alkyl)-benzyl (optionally substituted with halo (such as chloro)), optionally substituted
 20 phenoxymethyl, phenylsulphonylmethyl, benzyloxy, naphthyl or optionally substituted phenyl
 where said optional substituents are chosen from one or more halo.

Preferably R⁷ is benzyl, optionally substituted phenoxymethyl,
 phenylsulphonylmethyl, benzyloxy, naphthyl or optionally substituted phenyl where said
 optional substituents are chosen from one or more halo.

25 More preferably R⁷ is benzyl, phenoxymethyl optionally substituted with chloro,
 phenylsulphonylmethyl, benzyloxy, naphthyl or phenyl optionally substituted with chloro.

Particularly R⁷ is benzyl, 2,4,6-trichlorophenoxymethyl, phenylsulphonylmethyl,
 benzyloxy, naphthyl or 2,4-dichlorophenyl.

More particularly R⁷ is benzyl, 2,4,6-trichlorophenoxymethyl, phenylsulphonylmethyl,
 30 benzyloxy, naphth-2-yl or 2,4-dichlorophenyl.

Preferably (AA³) is Leu(S), Phe(S) optionally substituted with C₁₋₆alkyl or halo and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group or the sulphur moiety in the α -position of the amino acid (AA) may be optionally oxidised to form an -S(O)₂- or Phe(CH₂S).

5 More preferably (AA³) is Leu(S), Phe(S), 4-Cl-Phe(S), 3-Cl-Phe(S), 2-Cl-Phe(S), 3-Me-Phe(S), 4-F-Phe(S), Phe(S) fused to another phenyl group to form a naphth-1-yl group, Phe(S) fused to another phenyl group to form a naphth-2-yl group, 4-F-Phe(S) wherein the (S) is oxidised to S(O)₂, 3-Cl-Phe(S) wherein the (S) is oxidised to S(O)₂, 2-Cl-Phe(S) wherein the (S) is oxidised to S(O)₂, 4-Cl-Phe(S) wherein the (S) is oxidised to S(O)₂ or Phe(CH₂S).

10 Preferably R⁶ is hydrogen or a 5 membered heteroaryl ring containing a maximum of four heteroatoms. The heteroatoms are, for example, nitrogen, oxygen or sulphur. The 5 membered heteroaryl ring is, for example, thienyl, furyl, pyrazolyl, imidazolyl or 1,2,4-triazolyl.

Alternatively R⁶ is hydrogen, optionally substituted phenyl or a 5 membered heteroaryl
15 ring containing a maximum of four heteroatoms. The heteroatoms are, for example, nitrogen, oxygen or sulphur. The 5 membered heteroaryl ring is, for example, thienyl, furyl, pyrazolyl, imidazolyl or 1,2,4-triazolyl. Optional substituents include C₁₋₄ alkoxy (such as methoxy).

The variable R⁶ is, for example, methoxyphenyl.

More preferably R⁶ is hydrogen or thienyl.

20 Particularly R⁶ is hydrogen or thien-2-yl.

More particularly R⁶ is thien-2-yl.

In another aspect of the invention preferably R⁶ is an optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms wherein said optional substituents are as defined hereinbefore.

25 In another aspect of the invention more preferably R⁶ is an optionally substituted 5 membered heteroaryl ring containing a maximum of four heteroatoms wherein said optional substituents are as defined hereinbefore.

Preferred compounds are those of Examples 1 - 58 or a pharmaceutically acceptable salt thereof.

30 Especially preferred compounds are those of Examples 8, 13, 15, 17, 19, 25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40 and 41 or a pharmaceutically acceptable salt thereof.

Preferred compounds are those of Examples 59-66 or a pharmaceutically acceptable salt thereof. Especially preferred compounds are those of Examples 59-65.

Preferred compounds are those of Examples 67-74 and 97-113 or a pharmaceutically acceptable salt thereof.

5 Suitable pharmaceutically acceptable salts include acid addition salts such as the methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example a sodium salt, an alkaline earth metal salt for example a calcium or a magnesium salt, an organic amine salt for example a salt with triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or an amino acid for example a lysine salt. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

15 Some compounds of formula (I) may possess chiral centres. It is to be understood that the invention encompasses all such optical isomers and diastereoisomers of compounds of formula (I) which possess cysteine protease inhibitory activity.

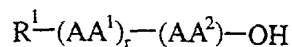
The invention further relates to all tautomeric forms of the compounds of formula (I).

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

20 Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof. According to this aspect of the invention there is provided a process (in which variable groups are as defined for formula (I) unless otherwise stated) which comprises:

25

a) coupling an acid of formula (III):

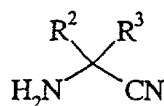


(III)

or a reactive derivative thereof;

30 with an amine of formula (IV):

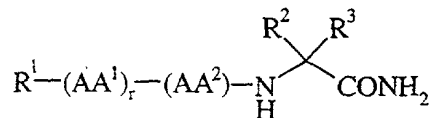
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(IV)

- A suitable reactive derivative of an acid of the formula (III) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate, an alcohol such as 1-hydroxybenzotriazole or a uronium salt such as 2-(1-benzotriazolyl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V); an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as *N,N*-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.
- The reaction is preferably carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide or hydroxide, for example sodium carbonate or potassium carbonate, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo-[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, acetonitrile, tetrahydrofuran, 1,2-dimethoxyethane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

- b) dehydrating a compound of formula (V):



(V)

under standard conditions.

For example such a dehydration reaction may conventionally be carried out by reaction with a reagent such as trifluoroacetic anhydride. The reaction can conveniently be conducted in the presence of a suitable base as defined hereinbefore such as, for example, triethylamine. The reaction is also preferably carried out in a suitable inert solvent or diluent, as defined
 5 hereinbefore such as dichloromethane and at a temperature in the range, for example, -10°C to reflux conveniently 10°C to reflux.

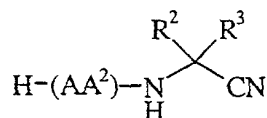
c) for compounds of formula (I) where $r = 1$, coupling an acid of formula (VI):



10

(VI)

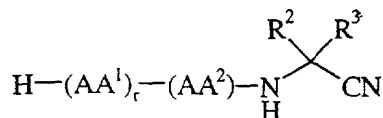
or a reactive derivative thereof as defined hereinbefore;
 with an amine of formula (VII):



(VII)

15 The reaction can conveniently be conducted under standard coupling conditions, such as those described in a) above.

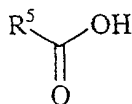
d) For compounds of formula (I) where R^1 is a group of formula (II) reaction of an amine of formula (VIII):



20

(VIII)

with an acid of formula (IX):



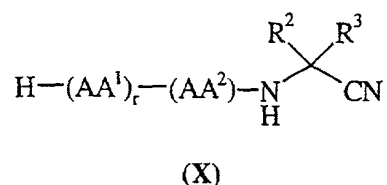
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(IX)

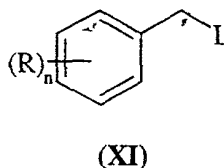
or a reactive derivative thereof as defined hereinbefore.

The reaction can conveniently be conducted under standard coupling conditions, such as those described in a) above.

- e) Compounds of formula (I) where R¹ is optionally substituted benzyl may be obtained by
 5 reaction of an amine of formula (X):



- i) with a compound of formula (XI):

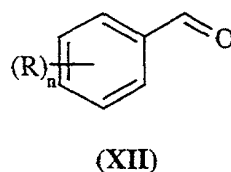


where (R)_n are optional substituents as defined above and L is a displaceable group.

A suitable displaceable group L is, for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

- 15 This reaction may be carried out under standard conditions such as, for example, those described in *Synthesis* **1993**, 12, 1243-6; or

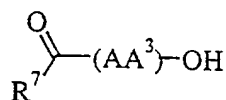
- ii) by reaction with an aldehyde of formula (XII):



- 20 This reaction may be carried out under standard conditions such as, for example, those described in *Synth. Commun.*, **1995**, 25, 18, 2819-2827.

- Another aspect of the present invention provides a process for preparing a compound of formula (Ia) or a pharmaceutically acceptable salt thereof. According to this aspect of the invention there is provided a process (in which variable groups are as defined for formula (Ia) unless otherwise stated) which comprises:
 25 a) coupling an acid of formula (IIIa):

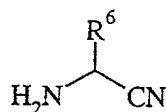
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(IIIa)

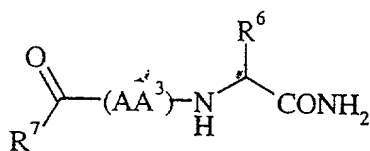
or a reactive derivative thereof;

with an amine of formula (IVa):



(IVa)

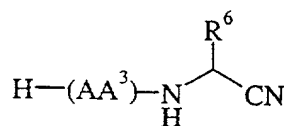
b) dehydrating a compound of formula (Va):



(Va)

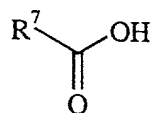
10 under standard conditions; or,

c) reaction of an amine of formula (VIa):



(VIa)

with an acid of formula (VIIa):



(VIIa)

or a reactive derivative thereof (as defined hereinbefore). These processes can be conducted as hereinbefore described.

If not commercially available, the necessary starting materials for the procedures described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, by techniques which are analogous to the above described procedures or by techniques which are analogous to the procedures described in the examples.

For example, it will be appreciated that certain of the optional substituents on a phenyl or naphthyl or a heteroaryl ring in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and a Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by, for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an

arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel, for example, those of the formula (V) and these are provided as a further feature of the invention. Moreover some of the starting materials for use in process variant (b) described hereinbefore, namely those compounds of the formula (VIII) are not only novel but also active as inhibitors of Cathepsin L and or Cathepsin S. Accordingly these compounds are provided as a further feature of the invention.

According to a further feature of the invention there is provided a compound of the formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

In order to use a compound of the formula (I) or (Ia) or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the

inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof,
5 and a pharmaceutically acceptable diluent or carrier.

In a further aspect the present invention provides a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, for use as a medicament.

In a still further aspect the present invention provides the use of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, in the manufacture of a
10 medicament for use in the inhibition of a cysteine protease in a warm blooded animal, such as man.

In a still further aspect the present invention provides the use of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm
15 blooded animal, such as man.

A method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof.

According to a further feature of the present invention there is provided a method for
20 producing inhibition of a cysteine protease in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

In particular the invention provides the use of a compound of the formula (I) or (Ia) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a
25 medicament for use in the inhibition of Cathepsin S in a warm blooded animal, such as man.

In order to use a compound of the formula (I) or (Ia) or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

30 The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be

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formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral
5 administration in unit dosage form, for example a tablet or capsule which contains between 100 mg and 1 g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular
10 dose of 1 mgkg^{-1} to 100 mgkg^{-1} of the compound, preferably in the range of 5 mgkg^{-1} to 20 mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately
15 equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I) or (Ia), or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

20 (a)

| <u>Tablet I</u> | <u>mg/tablet</u> |
|-----------------------|------------------|
| Compound X. | 100 |
| Lactose Ph.Eur. | 179 |
| Croscarmellose sodium | 12.0 |
| Polyvinylpyrrolidone | 6 |
| Magnesium stearate | 3.0 |

(b)

| <u>Tablet II</u> | <u>mg/tablet</u> |
|-----------------------|------------------|
| Compound X | 50 |
| Lactose Ph.Eur. | 229 |
| Croscarmellose sodium | 12.0 |
| Polyvinylpyrrolidone | 6 |
| Magnesium stearate | 3.0 |

(c)

| <u>Tablet III</u> | <u>mg/tablet</u> |
|-----------------------|------------------|
| Compound X | 1.0 |
| Lactose Ph.Eur. | 92 |
| Croscarmellose sodium | 4.0 |
| Polyvinylpyrrolidone | 2.0 |
| Magnesium stearate | 1.0 |

5 (d)

| <u>Capsule</u> | <u>mg/capsule</u> |
|-----------------------|-------------------|
| Compound X | 10 |
| Lactose Ph.Eur. | 389 |
| Croscarmellose sodium | 100 |
| Magnesium stearate | 1. |

(e)

| <u>Injection I</u> | <u>(50 mg/ml)</u> |
|---------------------------|-------------------|
| Compound X | 5.0% w/v |
| Isotonic aqueous solution | to 100% |

10 Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

5

Inhibition of Cathepsin L and S.

The pharmaceutically-acceptable compounds of the present invention are useful in the inhibition of Cathepsin L and Cathepsin S, having a good activity *in vitro* against human Cathepsin L, human Cathepsin S and rabbit Cathepsin L.

10

Cathepsin L Assay

Recombinant human Cathepsin L was cloned and expressed in E Coli and purified using the method as described by Zeneca Limited, GB 2 306 961 A (published 14.05.1997).

Rabbit Cathepsin L was purified from rabbit liver as described by Maciewicz R. A. and Etherington D. J. (Biochem. J. (1988) 256, 433-440) except the liver homogenate supernatant was concentrated by fractionation with $(\text{NH}_4)_2\text{SO}_4$ (20-80% saturation), and the pellet taken up and dialysed against 20mM NaAcetate pH 5.5, 1mM ethylenediaminetetraacetic acid (EDTA). The supernatant was then applied to a CM Sepharose ion exchange column and Cathepsin L eluted by gradient elution (0.25-0.75M NaCl). Fraction activity was determined using the synthetic substrate NCBz-Phe-Arg-NHMec as described. Cathepsin L fractions were pooled and desalted on a Sephacryl S100 column. Active fractions were pooled, adjusted to 20% saturation $(\text{NH}_4)_2\text{SO}_4$ and concentrated on a phenyl sepharose column. The remaining purification steps were as described.

Cathepsin L activity was measured based on the method of Barrett and Kirschke (1981 Methods in Enzymology, **80**, 535-561), using the fluorogenic substrates NCBz-Phe-Arg-NHMec. Inhibitors were identified by their ability to decrease the generation of the fluorescent leaving group (NHMec). Briefly the assay was as follows:

rHuman Cathepsin L or rabbit Cathepsin L (0.025 pmoles) was pre-incubated with or without test compound in 0.1M sodium acetate buffer pH4.5, 10mM cysteine, 0.1% Brij 35 at 25°C for 15 minutes in a solid black 96 well plate. Synthetic substrate, 20µM NCBz-Phe-Arg-NHMec, was added and the mixture incubated at 37°C for 30 minutes. The reaction was stopped by the addition of 0.1M sodium chloroacetate pH 4.3. Fluorescence was determined

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using a Fluoroskan II plate reader; excitation 355nm, emission 460nm. Compound potency was determined from the raw fluorescence data by calculating the IC₅₀ against each enzyme using a PC graph drawing software package.

5 Cathepsin S assay.

Cloning and Expression of human Cathepsin S.

Recombinant human Cathepsin S was cloned and expressed in Baculovirus, by the following method. The cDNA sequence for human Cathepsin S is available in the EMBL database Accession Number M90696. This database sequence was used to prepare, by PCR
10 on mRNA from human tissues, a recombinant plasmid carrying an insert with a DNA sequence identical to that of Cathepsin S in the EMBL database (Acc No M90696). The techniques for mRNA isolation, PCR and cloning are standard techniques known by those skilled in the art. Sequence determination of the recombinant insert was carried out using established DNA sequencing techniques.

15 The PCR was done so as to introduce an EcoRI cloning site 5' of the 'ATG' of Cathepsin S and an XbaI cloning site 3' of the 'Stop' codon. The PCR product was cloned between the EcoRI and XbaI sites of the baculovirus transfer vector pFASTBAC-1 (Bac-to-Bac Expression System commercially available from Gibco BRL -Life Technologies (cat no 10359-016)). This recombinant construct was used to generate, by standard techniques, a
20 recombinant baculovirus capable of expressing preprocathepsin S.

Expression of recombinant Cathepsin S was tested for the baculoviral constructs by infection of two insect cell lines : Sf9 cells (ATCC No CRL-1711) and T.ni cells (Invitrogen, Cat No B855-02).

25 Purification of Cathepsin S

Method I.

Procathepsin S was found in the insect cell medium and acid activated. The medium was mixed with an equal volume of 100mM Sodium Acetate buffer pH 4.5, 5mM dithiothreitol (DTT) and 5mM EDTA and incubated for one hour at 37°C method of Maubach
30 et al (Eur. J. Biochem., 250, 745-750, 1997).

Method 2.

The pH of insect cell medium (10ml) containing procathepsin S was adjusted to 4.5 with glacial acetic acid and DTT and EDTA added to 5mM. The sample was then incubated at 37°C for 150min to enable conversion to the active enzyme. Ammonium sulphate was then added to 80% saturation and a pellet obtained by centrifugation. This pellet was redissolved in 2ml buffer A (100mM Tris, 500mM NaCl, 1mM EDTA, pH7.5) and mixed in a batchwise fashion with 100µl thiopropyl-Sepharose for 15min at 4°C. The non bound fraction was removed by a brief centrifugation and the gel washed with 2x1ml buffer A. Cathepsin S was then eluted by batch mixing with 0.4ml 20mM DTT in buffer A for 15min at 4°C.

Measurement of Cathepsin S Activity.

Cathepsin S activity was measured based on the method of Maubach et al (Eur. J. Biochem., 250, 745-750, 1997), using the fluorogenic substrate Z-Val-Val-Arg-NHMec. Inhibitors were identified by their ability to decrease the generation of the fluorescent leaving group (NHMec). Briefly the assay was as follows:

rHuman Cathepsin S (1.5 nmoles) was pre-incubated with or without compounds in 50mM Potassium phosphate buffer pH 6.0-6.2, 20mM Na₂EDTA, 0.1% Brij at 25°C for 5 minutes in a solid black 96 well plate. Synthetic substrate, 20µM Z-Val-Val-Arg-NHMec, was added and the mixture incubated at 30°C for 20 minutes. The reaction was stopped by the addition of 0.1M sodium chloroacetate pH 4.3. Fluorescence was determined using a Fluoroskan II plate reader; excitation 355nm, emission 460nm. Compound potency was determined from the raw fluorescence data by calculating the IC₅₀ against Cathepsin S using a PC graph drawing software package.

The following results were obtained on a standard *in-vitro* test system for the inhibition of Cathepsin L. The activity is described in terms of IC₅₀.

When tested in the above *in-vitro* tests the compounds of this invention give IC₅₀s in the range 1-10,000 nM.

The following data was obtained for Examples 1, 19 and 26:

| Example | IC ₅₀ (Human) (nM) | IC ₅₀ (Rabbit) (nM) |
|---------|-------------------------------|--------------------------------|
| 1 | | 297 |
| 19 | 38 | 38.27 |
| 26 | 5651 | |

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- 5 (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;
- (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;
- 10 (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SP";
- 15 (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;
- (vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- 20 (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 250 MHz using perdeuterio dimethyl sulphoxide (DMSO- δ_6) as the solvent unless otherwise stated;
- (viii) chemical symbols have their usual meanings; SI units and symbols are used;
- 25 (ix) solvent ratios are given in percentage by volume;
- (x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected

by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported;

(xi) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in

5 isolation of materials with different melting points in some preparations; and

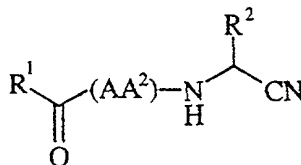
(xii) Z refers to benzyloxycarbonyl and Boc refers to *tert*-butoxycarbonyl.

Example 1

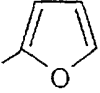
2-(Boc-L-phenylalanyl)-2-(2-furyl)acetonitrile

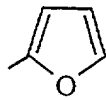
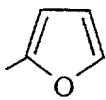
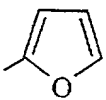
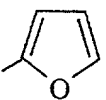
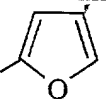
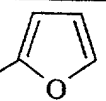
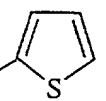
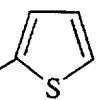
10 A mixture of Boc-L-phenylalanine (5.0 g), 2-(2-furyl)acetonitrile (3.0 g), hydroxybenzotriazole (5.1 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.0 g) and triethylamine (2.63 ml) in *N,N*-dimethylformamide (950 ml) was stirred at 0°C for 30 minutes and then at ambient temperature for 14 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and water 15 (100 ml). The ethyl acetate layer was separated and washed with 2M hydrochloric acid, brine, saturated aqueous sodium bicarbonate and dried. The residue obtained on removal of the solvent was subjected to chromatography on silica by elution with a mixture of dichloromethane and ethyl acetate (9:1 v/v) to give 2-(Boc-L-phenylalanyl)-2-(2-furyl)acetonitrile (4.53 g). Mp 157-158°C; m/z 370 (MH)⁺; NMR (CDCl₃) 1.4 (s, 9H), 3.1 (m, 20 2H), 4.37 (q, 1H), 4.87 (m, 1H), 6.1 (d, 1H), 6.39 (m, 1H), 6.45 (d, 1H), 6.72 (m, 1H), 7.22 (m, 5H), 7.41 (d, 1H).

Using this method but with appropriate starting materials there were prepared the following compounds:



25

| Example | R ¹ | AA ² | R ² | MH ⁺ | Mp (°C) |
|---------|-------------------|-----------------|---|-----------------|---------|
| 2 | ^t BuO- | Leu |  | 336 | |

| | | | | | |
|----|----------------------|-----------------------|---|-----|---------|
| 3 | Me | Leu |  | | 152-4 |
| 4 | Me | Leu |  | | 95-8 |
| 5 | ^t BuO- | Ile |  | | 106-8 |
| 6 | ^t BuO- | Val |  | | 106-9 |
| 7 | ^t BuO- | Leu | H | | 110-2 |
| 8 | PhCH ₂ O- | Tyr |  | 420 | |
| 9 | PhCH ₂ O- | Tyr(^t Bu) |  | | 97-100 |
| 10 | PhCH ₂ O- | Tyr |  | | 140 |
| 11 | PhCH ₂ O- | Phe |  | | 131-2 |
| 12 | ^t BuO- | Leu | Ph | 346 | 120-121 |

Example 13**(2S)-2-(Z-Leu-Leu-NH)-3-phenylpropionitrile**

- Trifluoroacetic anhydride (0.28 ml) was added dropwise to a mixture of Z-Leu-Leu-Phe-NH₂ (0.9 g) and pyridine (10 ml) which was stirred under argon at -10°C. The mixture was allowed to warm to room temperature over 1 hour, diluted with water and extracted with ethyl acetate. The extract was washed successively with 1M hydrochloric acid and brine, dried and evaporated to dryness and the residue was recrystallized from ethyl acetate/hexane to give (2S)-2-(Z-Leu-Leu-NH)-3-phenylpropionitrile (0.57 g). Mp 152-154°C; m/z 507 (MH)⁺;

Example 14-19:

- $$R^1-(AA^1)-(AA^2)-N\begin{matrix} R^2 \\ | \\ H \end{matrix}CN$$

| Example | R ¹ | AA ¹ | AA ² | R ² | Mp (°C) | MH ⁺ |
|-------------------|----------------|-----------------|-----------------|--------------------------------------|---------|-----------------|
| 14 ^{1,2} | BOC | Leu | Leu | MeSCH ₂ CH ₂ - | 129-130 | 457 |
| 15 ^{1,2} | Z | Leu | Leu | MeSCH ₂ CH ₂ - | - | 491 |
| 16 ^{1,2} | PhCO | Pyr-Ala | Leu | MeSCH ₂ CH ₂ - | - | 496 |
| 17 ^{1,3} | Z | Leu | Leu | i-PrS- | - | 491 |
| 18 ^{1,3} | Z | Phe | Leu | i-PrS- | - | 525 |
| 19 ^{1,3} | Z | Leu | Phe | i-PrS- | 163-165 | 525 |

10 (2S)-2-(Z-Phe-Leu-NH)-4-methylthiobutyronitrile

¹ Purified by flash chromatography on silica (Merck, ART 9385) using mixtures of ethyl acetate and hexane as eluent.

² S isomer at aminoacetonitrile.³ mixture of epimers at aminoacetonitrile

Example 21**(2S)-2-[(N-phenylacetyl-N-methyl-Leu)-Leu-NH]-4-methylthiobutyronitrile**

The process described in Example 20 was repeated using (2S)-2-[(N-phenylacetyl-N-methyl-Leu)-Leu-Met-NH₂] instead of Z-Phe-Leu-Met-NH₂ as starting material to give (2S)-2-
5 [(N-phenylacetyl-N-methyl-Leu)-Leu-NH]-4-methylthiobutyronitrile. M/z 489 (MH)⁺; NMR [at 100 °C] 0.9 (m, 12H), 1.4-1.8 (m, 6H), 2.0-2.2 (m, 5H), 2.55 (m, 2H), 2.95 (m, 3H), 3.75 (s, 2H), 4.35 (m, 1H), 4.75-5.0 (m, 2H), 7.1-7.5 (m, 6H), 8.25 (m, 1H).

Example 22**(2S)-2-[(N-benzoyl-N-methyl-Leu)-Leu-NH]-4-methylthiobutyronitrile**

The process described in Example 20 was repeated using (2S)-2-[(N-benzoyl-N-methyl-Leu)-Leu-Met-NH₂] instead of Z-Phe-Leu-Met-NH₂ as starting material to give (2S)-2-
10 [(N-benzoyl-N-methyl-Leu)-Leu-NH]-4-methylthiobutyronitrile. M/z 475 (MH)⁺; NMR [at 100 °C] 0.9 (m, 12H), 1.5-1.8 (m, 6H), 2.0-2.2 (m, 5H), 2.55 (m, 2H), 2.9 (m, 3H), 4.4 (m, 1H), 4.75-5.0 (m, 2H), 7.3-7.6 (m, 6H), 8.3 (m, 1H).
15

Example 23**(2S)-2-(Z-Leu-Leu-NH)-4-methylsulphonylbutyronitrile**

A mixture of (2S)-2-(Z-Leu-Leu-NH)-4-methylthiobutyronitrile (80 mg), oxone (150
20 mg), ethanol (2 ml) and water (1 ml) was stirred at room temperature for 18 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was dried and evaporated to dryness. The residue was purified by flash chromatography on silica (Merck, ART 9385) using increasingly polar mixtures of ethyl acetate and hexane as eluent to give
(2S)-2-(Z-Leu-Leu-NH)-4-methylsulphonylbutyronitrile (80 mg). M/z 489 (MH)⁺; NMR
25 (CDCl₃) 0.8-1.0 (m, 12H), 1.3-1.6 (m, 15H), 2.4 (m, 2H), 3.0 (s, 3H), 3.2 (m, 2H), 4.05 (m, 1H), 4.35 (m, 1H), 4.7-5.05 (m, 2H), 6.55 (d, 1H), 7.7 (d, 1H).

Example 24**(2RS)-2-(Z-Leu-Leu-NH)-2-phenylacetonitrile**

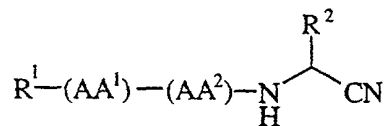
30 A mixture of (2RS)-2-(BOC-LeuNH)-2-phenylacetonitrile (0.69 g), dichloromethane (10 ml) and *N,N*-diisopropylethylamine (0.5 ml) was stirred under an argon atmosphere and iodotrimethylsilane (0.36 g) was added dropwise. The mixture was stirred for 1 hour and then

additional iodotrimethylsilane (0.36 g) was added and the mixture was stirred for a further hour. N-methylmorpholine (0.5 ml) was added followed by methanol (0.5 ml) and then the solution was evaporated to dryness.

- A mixture of the residue, *N,N*-dimethylformamide (10 ml), Z-LeuOH (0.58 g), 1-hydroxybenzotriazole (0.3 g), 1-dimethylaminopropyl-3-ethylcarbodiimide (0.42 g) and N-methylmorpholine (1 ml) was stirred at room temperature for 18 hours. The mixture was evaporated to dryness and the residue dissolved in ethyl acetate, and the solution was washed successively with 0.5M hydrochloric acid, 1M sodium hydroxide and brine and then dried and evaporated to dryness. The residue was purified by flash chromatography on silica (Merck, ART 9385) using increasingly polar mixtures of ethyl acetate and hexane as eluent to give (2*RS*)-2-(Z-Leu-Leu-NH)-phenylacetonitrile (0.45 g). Mp 168-170°C; *m/z* 493 (MH)⁺; NMR 0.75-0.95 (m, 12H), 1.25-1.75 (m, 6H), 4.05 (m, 1H), 4.4 (m, 1H), 5.0 (m, 2H), 6.15 (m, 1H), 7.3-7.5 (m, 11H), 7.95 (m, 1H), 9.15-9.3 (m, 1H).

15 Examples 25-29:

The following compounds were prepared by a similar process to that described in Example 24:



| Example | R ¹ | AA ¹ | AA ² | R ² | MH ⁺ |
|---------|----------------|-----------------|-----------------|----------------|-----------------|
| 25 | Boc | Leu | Leu | furan-2-yl | 449 |
| 26 | Boc | Leu | Phe | furan-2-yl | 483 |
| 27 | Boc | Leu | Ile | furan-2-yl | 449 |
| 28 | Boc | Leu | Val | furan-2-yl | 435 |
| 29 | Z | Leu | Leu | H | 417 |

20 Example 30

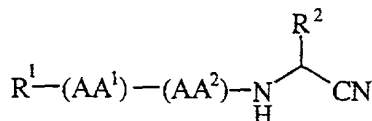
(2*RS*)-2-(Z-Leu-Leu-NH)-2-methoxyacetonitrile

N-bromosuccinimide (133 mg) was added to a stirred solution of (2*RS*)-2-(Z-Leu-Leu-NH)-2-(2-propylthio)acetonitrile (245 mg) in methanol (10 ml), the mixture was allowed to

- warm to room temperature and it was then stirred at room temperature for 1 hour. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and water. The ethyl acetate was dried and evaporated to dryness and the residue was purified by flash chromatography on silica (Merck, ART 9385) using increasingly polar mixtures of ethyl acetate and hexane as eluent and the product was recrystallized from carbon tetrachloride to give (2RS)-2-(Z-Leu-Leu-NH)-2-methoxyacetonitrile (190 mg). M/z 447 (MH)⁺; NMR 0.75-0.95 (m, 12H), 1.25-1.75 (m, 6H), 3.3 (s, 3H), 4.05 (m, 1H), 4.2-4.4 (m, 1H), 5.0 (s, 2H), 5.95 (m, 1H), 7.3-7.4 (m, 6H), 7.95 (m, 1H), 9.5-9.7 (m, 1H).

10 Example 31-33:

The following compounds were prepared by a similar process to that described in Example 30:



| Example | R ¹ | AA ¹ | AA ² | R ² | Mp (°C) | MH ⁺ |
|-------------------|----------------|-----------------|-----------------|----------------|---------|-----------------|
| 31 ⁴ | Z | Leu | Leu | i-PrO | | 475 |
| 32 ^{4,5} | Z | Leu | Leu | 2-propynyloxy | | 471 |
| 33 ^{4,5} | Z | Leu | Leu | Pyrazol-1-yl | 183-184 | 483 |

15 Example 34

(2RS)-2-(Z-Leu-Phe-NH)-2-(pyrazol-1-yl)acetonitrile

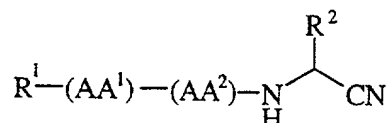
- A mixture of (2RS)-2-(Z-Leu-Phe-NH)-2-(2-propylthio)acetonitrile (105 mg), yellow mercuric oxide (100 mg), pyrazole and tetrahydrofuran (5 ml) was stirred at room temperature for 18 hours. The mixture was filtered and the filtrate was dried and evaporated to dryness.
- The residue was purified by flash chromatography on silica (Merck, ART 9385) using increasingly polar mixtures of ethyl acetate and hexane as eluent and the product was recrystallized from a mixture of dichloromethane and hexane to give (2RS)-2-(Z-Leu-Phe-NH)-2-(pyrazol-1-yl)acetonitrile (70 mg). Mp 189-192 °C; m/z 517 (MH)⁺; NMR 0.75-0.95 (m, 6H), 1.2-1.7 (m, 3H), 2.7-3.1 (m, 2H), 4.0 (m, 1H), 4.6 (m, 1H), 5.05 (s, 2H), 6.35 (m,

⁴ mixture of epimers at aminoacetonitrile (NB varying ratios of isomers)

1H), 7.0-7.5 (m, 12H), 7.65 (m, 1H), 7.7-7.85 (m, 1H), 7.95-8.1 (m, 1H), 10.05-10.25 (m, 1H).

Examples 35-38:

- 5 The following compounds were prepared by a similar process to that described in Example 34:



| Example | R ¹ | AA ¹ | AA ² | R ² | MH ⁺ |
|---------|----------------|-----------------|-----------------|-----------------------------------|-----------------|
| 35 | Z | Leu | Leu | imidazol-1-yl | 483 |
| 36 | Z | Leu | Leu | 1,2,4-triazol-1-yl ^f | 484 |
| 37 | Z | Leu | Leu | 3,5-dimethyl-pyrazol-1-yl | 511 |
| 38 | Z | Leu | Leu | 4-bromo-3,5-dimethyl-pyrazol-1-yl | 589 |

Example 39

10 2-(Z-Leu-Cha-NH)acetonitrile

- A mixture of Z-Leu-Cha-OH (0.95 g), aminoacetonitrile hydrochloride (0.23 g), 1-hydroxybenzotriazole (0.46 g), 1-dimethylaminopropyl-3-ethylcarbodiimide (0.5 g), *N,N*-dimethylformamide (6 ml) and *N*-methylmorpholine (0.75 ml) was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, and the solution was washed successively with 0.5 M hydrochloric acid, 1M sodium hydroxide and brine and then dried and evaporated to dryness. The residue was purified by flash chromatography on silica (Merck, ART 9385) using a 49:1 v:v mixture of dichloromethane and methanol as eluent and fractions containing the required product were collected, dried and evaporated to dryness. The residue was triturated with ether and the insoluble white solid collected to give 2-(Z-Leu-Cha-NH)acetonitrile (0.46 g). M/z 493 (MH)⁺; NMR 0.75-0.95 (m, 6H), 1.0-1.8 (m, 14H), 4.0-4.2 (m, 3H), 4.35 (q, 1H), 5.05 (s, 2H), 7.25-7.5 (m, 6H), 7.95 (d, 1H), 8.6 (m, 1H).

^f 5 equivalents of alcohol/pyrazole in tetrahydrofuran solution and 18 hours reaction time.

Example 40**2-[[2-(4-Pyridyl)acetyl]-Leu-Leu]-4-methylthiobutyronitrile**

A mixture of 2-(H-Leu-Leu-NH)-4-methylthiobutyronitrile (71 mg), 1-hydroxybenzotriazole (34 mg), 1-dimethylaminopropyl-3-ethylcarbodiimide (48 mg), 2-(4-pyridyl)acetic acid hydrochloride (35 mg), *N,N*-dimethylformamide (2 ml) and *N*-methylmorpholine (0.2 ml) was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, and the solution was washed successively with 1M sodium hydroxide and brine, dried and evaporated to dryness. The residue was recrystallized from ethyl acetate to give 2-[[2-(4-pyridyl)acetyl]-Leu-Leu]-4-methylthiobutyronitrile (42 mg). Mp 177-178 °C; M/z 476 (MH)⁺; NMR 0.75-0.95 (m, 12H), 1.3-1.7 (m, 6H), 1.9-2.1 (m, 5H), 2.5 (m, 2H), 3.5 (s, 2H), 4.15-4.4 (m, 2H), 4.85 (q, 1H), 7.25 (d, 2H), 8.1 (d, 1H), 8.35 (d, 1H), 8.45 (d, 2H), 8.65 (d, 1H).

Example 41**Ac-Leu-Leu-(2-furyl)acetonitrile**

Trimethylsilyl iodide (0.7 ml) was added to a solution of Boc-Leu-Leu-(2-furyl)-acetonitrile (1.68 g) in chloroform (50 ml) at 0°C. The mixture was stirred at 0°C for 15 minutes and the solvent was removed under reduced pressure. The residue was dissolved in pyridine (20 ml), the solution was cooled to 0°C and acetic anhydride (20 ml) was added and the reaction mixture was stirred at ambient temperature for 14 hours. The reaction mixture was evaporated to dryness and the residue was dissolved in ethyl acetate (100 ml) and washed with 2M hydrochloric acid, brine, saturated aqueous sodium bicarbonate solution, brine and dried. The residue obtained on removal of the solvent was triturated with diethyl ether and filtered. The solid was dissolved in warm acetone, treated with activated charcoal and filtered. The solvent was removed to give Ac-Leu-Leu-(2-furyl)acetonitrile (0.64 g). Mp 235-242°C; m/z 391 (MH)⁺; NMR 0.88 (m, 12H), 1.51 (m, 6H), 1.83 (d, 3H), 4.29 (m, 2H), 6.23 (d, 1H), 6.53 (m, 2H), 7.76 (m, 1H), 7.95 (m, 2H), 9.19 (m, 1H).

Example 42**(2S)-2-(Boc-Leu-NH)isovaleronitrile**

Trifluoroacetic anhydride (0.84 g) was added dropwise to a mixture of BOC-Leu-Leu-NH₂ (1 g) and pyridine (10 ml) which was stirred under argon at -10°C. The mixture was

allowed to warm to room temperature over 1 hour, diluted with water and extracted with diethyl ether. The extract was washed successively with 1M hydrochloric acid and brine, dried and evaporated to dryness. The residue was recrystallized from ether/hexane to give (2S)-2-(BOC-Leu-NH)isovaleronitrile (0.66 g). Mp 117-118°C; m/z 326 (MH)⁺.

5

Example 43**(2S)-2-(Boc-Leu-NH)-4-methylthiobutyronitrile**

The process described in Example 42 was repeated using BOC-Leu-Met-NH₂ instead of BOC-Leu-Leu-NH₂ to give (2S)-2-(BOC-Leu-NH)-4-methylthiobutyronitrile. Mp 69-71°C; m/z 344 (MH)⁺.

10

Example 44**(2S)-2-[(N-4-chlorobenzyl)-Leu]-Leu-NH]-4-methylthiobutyronitrile**

A mixture of (2S)-2-[H-Leu-Leu-NH]-4-methylthiobutyronitrile (90mg), ethanol (5ml) and 4-chlorobenzaldehyde was stirred at ambient temperature for 1 hour. Acetic acid (0.05ml) was added followed by sodium cyanoborohydride (50mg) and stirring was continued for a further 3 hours. Acetic acid (0.2ml) was added and the mixture was left at room temperature for 16 hours. The mixture was diluted with water and basified with sodium hydrogen carbonate then extracted with ethyl acetate. The extract was dried and evaporated to dryness and the residue was purified by flash chromatography on silica (Merck, ART 9385) using increasingly polar mixtures of ethyl acetate and hexane as eluent to give (2S)-2-[(N-4-chlorobenzyl)-Leu]-Leu-NH]-4-methylthiobutyronitrile as a gum (102mg). The gum was dissolved in ethyl acetate and the solution was acidified with ethereal HCl. The mixture was evaporated to dryness and the residue was triturated with ethyl acetate and the insoluble solid collected to give (2S)-2-[(N-4-chlorobenzyl)-Leu]-Leu-NH]-4-methylthiobutyronitrile hydrochloride (75mg). Mp 146-147°C; NMR 0.9 (m, 12H), 1.4-1.8 (m, 6H), 2.0-2.2 (m, 5H), 2.55(m, 2H), 3.6 (m, 1H), 3.7-4.2 (m, 2H), 4.35 (m, 1H), 4.85 (m, 1H), 7.5(m, 4H), 8.9-9.1 (m, 2H), 9.45 (m, 1H), 9.7 (m, 1H); m/z 481 (MH)⁺.

15

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25

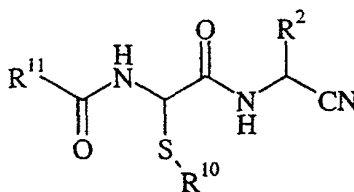
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Example 45**2-[2-benzyloxycarbonylamino-2-phenylthioacetamido]-2-(2-thienyl)-acetonitrile**

A mixture of 2-benzyloxycarbonylamino-2-phenylthioacetic acid (160mg), 2-amino-2-(2-thienyl)acetonitrile hydrochloride (88 mg), hydroxybenzotriazole (75 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (105 mg) and 4-methylmorpholine (0.15 ml) in *N,N*-dimethylformamide (3 ml) was stirred at ambient temperature for 48 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The ethyl acetate layer was separated and washed with 2M hydrochloric acid, brine, saturated aqueous sodium bicarbonate and dried and evaporated to dryness. The residue was purified by flash chromatography on silica (Merck, ART 9385) using increasingly polar mixtures of ethyl acetate and hexane as eluent followed by recrystallisation from a mixture of ethyl acetate and hexane to give 2-(2-benzyloxycarbonylamino-2-phenylthioacetamido)-2-(2-thienyl)-acetonitrile (4.53 g). M/z 438 (MH)⁺; NMR (CDCl₃) 5.1 (m, 2H), 5.5 (m, 1H), 5.85 (m, 1H), 6.2 (m, 1H), 6.8-7.1 (m, 2H), 7.2-7.55 (m, 12H).

Example 46 - 55

The following examples were prepared by a process similar to that described in Example 45:



20

| Example | R ¹¹ | R ¹⁰ | R ² | Mp (°C) | MH ⁺ |
|---------|---------------------------------|-----------------|----------------|---------|-----------------|
| 46 | benzyloxy | 2-propyl | H | - | 322 |
| 47 | benzyloxy | phenyl | H | - | 356 |
| 48 | benzyl | phenyl | H | - | 340 |
| 49 | 2,4,6-trichloro phenoxyethyl | phenyl | H | 153-154 | 458 |
| 50 | naphth-2-yl | phenyl | H | 151-153 | 376 |
| 51 | 2,4-dichlorophenyl | phenyl | H | 171-172 | 394 |

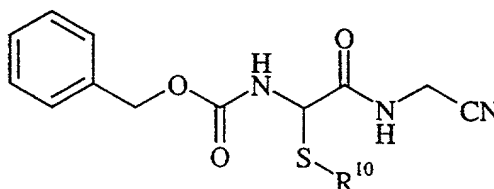
| | | | | | |
|----|---------------------------|-------------|-------------------|---------|-----|
| 52 | naphth-2-yl | naphth-1-yl | H | 190-192 | 426 |
| 53 | naphth-2-yl | naphth-2-yl | H | 186-188 | 426 |
| 54 | phenylsulphonyl methyl | phenyl | H | 189-190 | 404 |
| 55 | benzyloxy | m-tolyl | thiophen-2- yl | 118-121 | 452 |

Example 56**2-[2-benzyloxycarbonylamino-2-(4-chlorophenylthio)acetamido]-2-(2-thienyl)-acetonitrile**

- 5 A mixture of 2-[2-benzyloxycarbonylamino-2-(hydroxy)acetamido]-2-(2-thienyl)-
acetonitrile (132 mg), 1,2-dichloroethane (5 ml), 2-naphthalenesulphonic acid (5 mg) and 4-
chlorothiophenol (1.65 g) was stirred at reflux for 2 hours then cooled to room temperature
and evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was
washed successively with 1M NaOH and brine, dried and evaporated to dryness. The residue
was recrystallized from ethyl acetate and hexane to give 2-[2-benzyloxycarbonylamino-2-(4-
10 chlorophenylthio)acetamido]-2-(2-thienyl)-acetonitrile (80 mg). Mp 165-166°C; m/z 390
(MH)⁺; NMR 4.2 (d, 2H), 5.0 (q, 2 1H), 5.7 (d, 1H), 7.2-7.55 (m, 9H), 8.2 (d, 1H), 9.0 (t, 1H).

Examples 57-8

- The following examples were prepared by a process similar to that described in
15 Example 56:



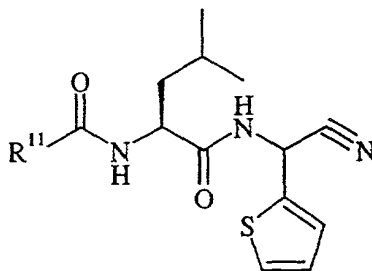
| Example | R ¹⁰ | Mp (°C) | MH ⁺ |
|---------|-----------------|---------|-----------------|
| 57 | 3-chlorophenyl | 149-150 | 390 |
| 58 | benzyl | 139-140 | 370 |

Example 59**N-(N-Morpholinocarbonyl)-(L)-leucyl-2-(2-thienyl)glycinenitrile**

A mixture of N-(N-morpholinocarbonyl)-(L)-leucine (Method M) (0.323 g), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.28 g) and 1-hydroxybenzotriazole (0.197 g) in N,N-dimethylformamide (50 ml) was stirred at ambient temperature for 30 minutes. 2-(2-Thienyl)-2-aminoacetonitrile (Method A1) (0.253 g) and N-methylmorpholine (160 μ l) were added and the mixture was stirred for 20 hours. The reaction mixture was evaporated to dryness (high vac) and the residue was suspended in saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (2x50 ml). The combined ethyl acetate extracts were washed successively with 10% citric acid and brine and dried. The residue obtained on removal of the solvent was chromatographed on a Bond-elut column eluting with a mixture of ethyl acetate and dichloromethane (1/1 v/v) to give the title compound (0.159 g) as a 1/1 mixture of diastereoisomers. NMR: 9.2-9.3 (1H), 7.6 (m, 1H), 7.2 (m, 1H), 7.0 (m, 1H), 6.5 (m, 1H), 6.3 (m, 1H), 4.2 (m, 1H), 3.45 (m, 4H), 3.3 (m, 4H), 1.6 (m, 2H), 1.4 (m, 1H), 0.8 (m, 6H).

Examples 60-63

Following the method outlined in Example 59 and using the appropriate acid chlorides there were prepared:



20

| Ex No. | R ¹¹ | (M+H) |
|--------|-----------------|-------|
| 60 | c-Hexyl | 362 |
| 61 | c-Pentyl | 348 |
| 62 | c-Hexylmethyl | 376 |
| 63 | N-Piperidiny | 363 |

Example 64**N-[(2-Phenylacetyl-amino-2-phenylthio)acetyl]-2-thienylaminoacetonitrile**

Carbonyl diimidazole (0.538g) was added to a solution of N-[(2-phenylacetyl-amino-2-phenylthio)acetic acid (1g) in THF (25 ml) and the mixture was stirred at 20 °C for 20 hours.

- 5 2-(2-Thienyl)-aminoacetonitrile (Method A1) (0.579 g) and triethylamine (0.664 g) were added and the mixture was stirred at 20 °C for 20 hours. The solvent was removed and the residue dissolved in dichloromethane (25 ml) and washed successively with aqueous sodium bicarbonate solution (2x20 ml) and 2M hydrochloric acid (2x20 ml). The solvent was removed and the residue was chromatographed on silica eluting with a mixture of ethyl
- 10 acetate and isohexane (35:100) to give the title compound.

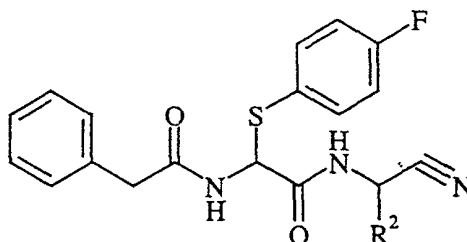
Diastereoisomer 1; Faster running fraction: Mp 172 °C; m/z 422 (M+H)⁺; NMR: 9.9 (d, 1H), 8.95 (d, 1H), 7.65 (m, 1H), 7.2 (m, 11H), 6.45 (d, 1H), 5.8 (d, 1H), 3.5 (m, 2H).

Diastereoisomer 2; Slower running fraction: Mp 159 °C; m/z 422 (M+H)⁺; NMR: 9.8 (d, 1H), 8.95 (d, 1H), 7.65 (m, 1H), 7.2 (m, 11H), 6.45 (d, 1H), 5.8 (d, 1H), 3.5 (m, 2H).

15

Examples 65-66

Following the method outlined in Example 64 and using the appropriate starting materials there were prepared:



| Ex No. | R ² | M.p. °C |
|-----------------|----------------|---------|
| 65 ¹ | 2-thienyl | 144 |
| 66 | H | 204 |

20 ¹ Mixture of diastereoisomers.

Example 67**N-[(2-Phenylacetyl-amino-2-phenylthio)acetyl]-2-thienylaminoacetonitrile**

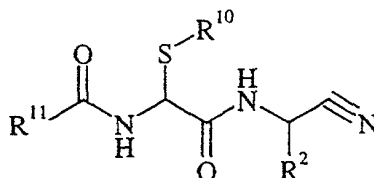
Carbonyl diimidazole (0.538g) was added to a solution of N-[(2-phenylacetyl-amino-2-phenylthio)acetic acid (Method O) (1g) in THF (25 ml) and the mixture was stirred at 20 °C for 20 hours. 2-(2-Thienyl)-aminoacetonitrile (Method A1) (0.579 g) and triethylamine (0.664 g) were added and the mixture was stirred at 20 °C for 20 hours. The solvent was removed and the residue dissolved in dichloromethane (25 ml) and washed successively with aqueous sodium bicarbonate solution (2x20 ml) and 2M hydrochloric acid (2x20 ml). The solvent was removed and the residue was chromatographed on silica eluting with a mixture of ethyl acetate and isohexane (35:100) to give the title compound.

Diastereoisomer 1; Faster running fraction: Mp 172 °C; m/z 422 (M+H)⁺; NMR: 9.9 (d, 1H), 8.95 (d, 1H), 7.65 (m, 1H), 7.2 (m, 1H), 6.45 (d, 1H), 5.8 (d, 1H), 3.5 (m, 2H).

Diastereoisomer 2; Slower running fraction: Mp 159 °C; m/z 422 (M+H)⁺; NMR: 9.8 (d, 1H), 8.95 (d, 1H), 7.65 (m, 1H), 7.2 (m, 1H), 6.45 (d, 1H), 5.8 (d, 1H), 3.5 (m, 2H).

Examples 68-96

Following the method outlined in Example 67 and using the appropriate starting materials there were prepared:



| Ex No. | R ² | R ¹⁰ | R ¹¹ | M.p. °C |
|-----------------|----------------|---|---|---------|
| 68 ¹ | 2-thienyl | 4-F-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 144 |
| 69 | H | 4-F-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 204 |
| 70 ² | 2-thienyl | 3-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 178 |
| 71 ³ | 2-thienyl | 3-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 182 |
| 72 | H | 3-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 207 |
| 73 | H | 2-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 156 |
| 74 | H | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 220 |
| 75 | H | C ₆ H ₅ CH ₂ | C ₆ H ₅ CH ₂ | 138 |

| | | | | |
|------|---|---|---|-----|
| 76 | H | C ₆ H ₅ CH ₂ CH ₂ | C ₆ H ₅ CH ₂ | 160 |
| 77 | 2-thienyl | C ₆ H ₅ CH ₂ | C ₆ H ₅ CH ₂ | 174 |
| 78 | 2-thienyl | C ₆ H ₅ CH ₂ CH ₂ | C ₆ H ₅ CH ₂ | 148 |
| 79 | H | 4-Cl-C ₆ H ₄ | 2-Cl-C ₆ H ₄ CH ₂ | 109 |
| 80 | H | 4-Cl-C ₆ H ₄ | 3-Cl-C ₆ H ₄ CH ₂ | 178 |
| 81 | H | 4-Cl-C ₆ H ₄ | 4-Cl-C ₆ H ₄ CH ₂ | 190 |
| 82 ‘ | 2-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 181 |
| 83 ‘ | 2-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 166 |
| 84 “ | 4-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 192 |
| 85 “ | 4-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 168 |
| 86 ^ | 2-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | 3-Cl-C ₆ H ₄ CH ₂ | 185 |
| 87 ^ | 2-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | 3-Cl-C ₆ H ₄ CH ₂ | 183 |
| 88 | 3-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | 3-Cl-C ₆ H ₄ CH ₂ | 168 |
| 89 | 4-CH ₃ O-C ₆ H ₄ | 4-Cl-C ₆ H ₄ | 3-Cl-C ₆ H ₄ CH ₂ | 158 |
| 90 ~ | H | 4-Cl-C ₆ H ₄ | <u>R</u> -C ₆ H ₅ CH(CH ₃) | 151 |
| 91 ~ | H | 4-Cl-C ₆ H ₄ | <u>R</u> -C ₆ H ₅ CH(CH ₃) | 161 |
| 92 @ | H | 4-Cl-C ₆ H ₄ | <u>S</u> -C ₆ H ₅ CH(CH ₃) | 153 |
| 93 @ | H | 4-Cl-C ₆ H ₄ | <u>S</u> -C ₆ H ₅ CH(CH ₃) | 158 |
| 94 # | H | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH(CH ₂ CH ₃) | 165 |
| 95 # | H | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH(CH ₂ CH ₃) | 179 |
| 96 | H | 4-Cl-C ₆ H ₄ | 4-Cl-C ₆ H ₄ C(CH ₃) ₂ | |

¹ Mixture of diastereoisomers.

² Diastereoisomer 1; Faster running fraction.

³ Diastereoisomer 2; Slower running fraction.

*, ‘, “, ^, ~, @, # Pairs of diastereoisomers.

5 Example 97

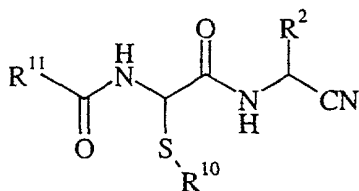
2-[2-benzyloxycarbonylamino-2-phenylthioacetamido]-2-(2-thienyl)-acetonitrile

A mixture of 2-benzyloxycarbonylamino-2-phenylthioacetic acid (Method P) (160mg), 2-amino-2-(2-thienyl)acetonitrile hydrochloride (Method A1) (88 mg), hydroxybenzotriazole (75 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (105 mg) and 4-methylmorpholine (0.15 ml) in *N,N*-dimethylformamide (3 ml) was stirred at ambient

temperature for 48 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The ethyl acetate layer was separated and washed with 2M hydrochloric acid, brine, saturated aqueous sodium bicarbonate and dried and evaporated to dryness. The residue was purified by flash chromatography on silica (Merck, ART 9385) using increasingly polar mixtures of ethyl acetate and hexane as eluent followed by recrystallisation from a mixture of ethyl acetate and hexane to give 2-(2-benzyloxycarbonylamino-2-phenylthioacetamido)-2-(2-thienyl)-acetonitrile (4.53 g). M/z 438 (MH^+); NMR ($CDCl_3$) 5.1 (m, 2H), 5.5 (m, 1H), 5.85 (m, 1H), 6.2 (m, 1H), 6.8-7.1 (m, 2H), 7.2-7.55 (m, 12H).

Example 98-107

The following examples were prepared by a process similar to that described in Example 97:



15

| Example | R ¹¹ | R ¹⁰ | R ² | Mp (°C) | MH ⁺ |
|---------|---------------------------------|-----------------|----------------|---------|-----------------|
| 98 | benzyloxy | 2-propyl | H | - | 322 |
| 99 | benzyloxy | phenyl | H | - | 356 |
| 100 | benzyl | phenyl | H | - | 340 |
| 101 | 2,4,6-trichloro phenoxyethyl | phenyl | H | 153-154 | 458 |
| 102 | naphth-2-yl | phenyl | H | 151-153 | 376 |
| 103 | 2,4-dichlorophenyl | phenyl | H | 171-172 | 394 |
| 104 | naphth-2-yl | naphth-1-yl | H | 190-192 | 426 |
| 105 | naphth-2-yl | naphth-2-yl | H | 186-188 | 426 |
| 106 | phenylsulphonyl methyl | phenyl | H | 189-190 | 404 |

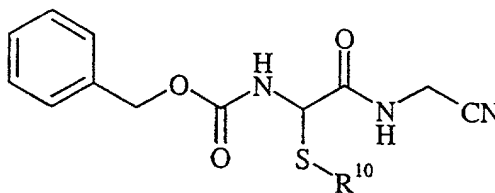
| | | | | | |
|-----|-----------|---------|---------------|---------|-----|
| 107 | benzyloxy | m-tolyl | thiophen-2-yl | 118-121 | 452 |
|-----|-----------|---------|---------------|---------|-----|

Example 1082-[2-benzyloxycarbonylamino-2-(4-chlorophenylthio)acetamido]-2-(2-thienyl)-acetonitrile

- 5 A mixture of 2-[2-benzyloxycarbonylamino-2-(hydroxy)acetamido]-2-(2-thienyl)-acetonitrile (Method R) (132 mg), 1,2-dichloroethane (5 ml), 2-naphthalenesulphonic acid (5 mg) and 4-chlorothiophenol (1.65 g) was stirred at reflux for 2 hours then cooled to room temperature and evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed successively with 1M NaOH and brine, dried and evaporated to dryness.
- 10 The residue was recrystallized from ethyl acetate and hexane to give 2-[2-benzyloxycarbonylamino-2-(4-chlorophenylthio)acetamido]-2-(2-thienyl)-acetonitrile (80 mg). Mp 165-166°C; m/z 390 (MH)⁺; NMR 4.2 (d, 2H), 5.0 (q, 2 1H), 5.7 (d, 1H), 7.2-7.55 (m, 9H), 8.2 (d, 1H), 9.0 (t, 1H).

15 **Examples 109-110**

The following examples were prepared by a process similar to that described in Example 108:



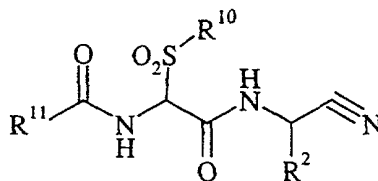
| Example | R ¹⁰ | Mp (°C) | MH ⁺ |
|---------|-----------------|---------|-----------------|
| 109 | 3-chlorophenyl | 149-150 | 390 |
| 110 | benzyl | 139-140 | 370 |

Example 111**N-[(2-Phenylacetyl-amino-2-(4-fluorophenylsulphonyl))acetyl] aminoacetonitrile**

m-Chloroperbenzoic acid (578 mg) was added to a suspension of N-[(2-Phenylacetyl-amino-2-(4-fluorophenylthio))acetyl]aminoacetonitrile (Example 69) (300 mg) in dichloromethane (30 ml) and the mixture was stirred at room temperature for 3 hours then washed successively with aqueous sodium bicarbonate (3 x 10 ml), aqueous sodium thiosulphate (1 x 10 ml) and the organic layer was collected and dried. The residue obtained on removal of the solvent was triturated with diethyl ether to give the title compound Mp 175°C; NMR 9.39 (t, 1H), 9.3 (d, 1H), 7.75 (m, 2H), 7.3 (m, 7H), 6.05 (d, 1H), 4.29 (d, 2H), 3.5 (q, 2H).

Examples 112-116

Following the method outlined in Example 111 and using the appropriate starting materials there were prepared:



| Ex No. | R ² | R ¹⁰ | R ¹¹ | M.p. °C |
|--------|----------------|------------------------------------|--|---------|
| 112 | H | 3-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 202 |
| 113 | H | 4-Cl-C ₆ H ₄ | C ₆ H ₅ CH ₂ | 210 |
| 114 | H | C ₆ H ₅ | C ₆ H ₅ CH ₂ | 192 |
| 115 ** | H | 4-Cl-C ₆ H ₄ | <u>S</u> -C ₆ H ₅ CH(CH ₃) | 185 |
| 116 ** | H | 4-Cl-C ₆ H ₄ | <u>S</u> -C ₆ H ₅ CH(CH ₃) | 188 |

** Pair of diastereomers

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method A**2-(2-Furyl)-2-aminoacetonitrile**

Ammonium chloride (25 g) was added to a solution of 2-furfuraldehyde (25 g) in diethyl ether (250 ml). A solution of sodium cyanide (17 g) in water (80 ml) was added over
 5 20 minutes. The reaction mixture was stirred at ambient temperature for 14 hours, the aqueous layer was removed and the organic layer was washed twice with saturated aqueous sodium hydrogen carbonate solution (100 ml each time), dried and evaporated to dryness. The residue was dissolved in diethyl ether (250 ml) and cooled to 0 °C. Hydrogen chloride gas was
 10 bubbled through the solution keeping the temperature below 10 °C. 2-(2-Furyl)-2-aminoacetonitrile hydrochloride was filtered and dried, yield 33 g. ¹H NMR 6.19 (s, 1H), 6.56 (m, 1H), 6.78 (d, 1H), 7.83 (m, 1H), 9.83 (broad s, 2H).

Method A1

Following the method outlined in Method A and using the appropriate aldehyde there was prepared:

15 **A1 2-(2-thienyl)-2-aminoacetonitrile hydrochloride**

Method B**Z-Leu-Leu-Phe-NH₂**

A mixture of H-Leu-Phe-NH₂ hydrochloride (0.8 g), Z-Leu-OH (0.72 g), *N,N*-dimethylformamide (10 ml), 1-hydroxybenzotriazole (0.41 g), 1-dimethylaminopropyl-3-
 20 ethylcarbodiimide hydrochloride (0.57 g) and *N*-methylmorpholine (1 ml) was stirred at room temperature for 18 hours. The mixture was evaporated to dryness and the residue stirred with water and ethyl acetate. The insoluble solid was collected to give Z-Leu-Leu-Phe-NH₂ (0.67 g). *M/z* 525 (MH)⁺.

Method B1

25 Following the method outlined in Method C and using the appropriate protected starting materials there was prepared:

| Method | Product | Starting Materials | (MH) ⁺ |
|--------|-------------------------------|--|-------------------|
| B1 | Z-Phe-Leu-Met-NH ₂ | H-Leu-Met-NH ₂ and Z-Phe-OH | 543 |

Method C**Boc-Leu-Met-NH₂**

A mixture of Leu-Met-NH₂ hydrochloride (0.45 g), BOC-Leu-OH (0.35 g), *N,N*-dimethylformamide (5 ml), 1-hydroxybenzotriazole (0.23 g), dicyclohexylcarbodiimide (0.35 g) and *N*-methylmorpholine (0.2 ml) was stirred at room temperature for 18 hours. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate. The solution was washed successively with 0.5 M hydrochloric acid, 1M sodium hydroxide and brine, dried and evaporated to dryness. The residue was recrystallized from a mixture of ethyl acetate and hexane to give BOC-Leu-Met-NH₂ (0.45 g). Mp 145-147°C; m/z 475 (MH)⁺.

Methods C1-2

Following the method outlined in Method C and using the appropriate protected amino acid there was prepared:

| Method | Product | Amino Acid | (MH) ⁺ |
|--------|---|--------------------------------------|-------------------|
| C1 | Z-Leu-Leu-Met-NH ₂ | Z-Leu-OH | 509 |
| C2 | [(2RS)-N-benzoyl-3-(4-pyridyl)alaninyl]-Leu-Met-NH ₂ | (2RS)-N-benzoyl-3-(4-pyridyl)alanine | 509 |

Method D**2-(2-propylthio)-2-(Z-Leu-Phe-NH)acetic acid**

A mixture of Z-Leu-Phe-NH₂ (3 g), glyoxylic acid monohydrate (0.83 g) and dioxan (20 ml) was stirred at reflux for 18 hours, cooled and evaporated to dryness. The residue was treated with dichloroethane (20 ml), 2-propane thiol (2.25 g) and naphthalene-2-sulphonic acid (50 mg) and the mixture was stirred at 60°C for 4 hours and then evaporated to dryness. The residue was stirred with ether and the insoluble white solid was collected to give 2-(2-propylthio)-2-(Z-Leu-Phe-NH)acetic acid (2.1 g). Mp 156-158°C; m/z 544 (MH)⁺.

Methods D1-2

Following the method outlined in Method D and using the appropriate dipeptide there was prepared:

| Method | Product | Dipeptide |
|--------|--|---------------------------|
| D1 | 2-(2-propylthio)-2-(Z-Leu-Leu-NH)acetic acid | Z-Leu-Leu-NH ₂ |

| | | |
|----|--|---------------------------|
| D2 | 2-(2-propylthio)-2-(Z-Phe-Leu-NH)acetic acid | Z-Phe-Leu-NH ₂ |
|----|--|---------------------------|

Method E**2-(2-propylthio)-2-(Z-Leu-Phe-NH)acetamide**

- A mixture of 2-(2-propylthio)-2-(Z-Leu-Phe-NH)acetic acid (2 g), ammonium chloride (0.54 g), *N,N*-dimethylformamide (15 ml), 1-hydroxybenzotriazole (0.67 g), 1-dimethylaminopropyl-3-ethylcarbodiimide (0.95 g) and *N*-methylmorpholine (2 ml) was stirred at room temperature for 18 hours. The mixture was evaporated to dryness and the residue taken up in ethyl acetate. The solution was washed successively with 0.5 M hydrochloric acid, 1 M sodium hydroxide and brine. The solid which separated from the ethyl acetate phase was collected to give 2-(2-propylthio)-2-(Z-Leu-Phe-NH)acetamide, (1 g).
- Mp 198-201°C; m/z 543 (MH)⁺.

Methods E1-2

Following the method outlined in Method E and using the appropriate acetic acid there was prepared:

| Method | Product | Acetic Acid | (MH) ⁺ |
|--------|--|--|-------------------|
| E1 | 2-(2-propylthio)-2-(Z-Leu-Leu-NH)acetamide | 2-(2-propylthio)-2-(Z-Leu-Leu-NH)acetic acid | 509 |
| E2 | 2-(2-propylthio)-2-(Z-Phe-Leu-NH)acetamide | 2-(2-propylthio)-2-(Z-Phe-Leu-NH)acetic acid | 543 |

Method F**Z-Leu-Cha-OH**

- A mixture of Z-Leu-OH (2.77 g), (S)-3-cyclohexylalanine methyl ester hydrochloride (1.92 g), 1-hydroxybenzotriazole (1.76 g), 1-dimethylaminopropyl-3-ethylcarbodiimide (1.92 g), *N,N*-dimethylformamide (10 ml) and *N*-methylmorpholine (3 ml) was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, and the solution was washed successively with 0.5 M hydrochloric acid, 1M sodium hydroxide and brine, then dried and evaporated to dryness. The residue was stirred in a mixture of tetrahydrofuran (15 ml) and 1M sodium hydroxide for 1 hour at room temperature. The mixture was acidified with 2M hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried and evaporated to dryness to give Z-Leu-Cha-OH. M/z 419 (MH)⁺.

Method G**(2S)-2-(H-Leu-Leu-NH)-4-methylthiobutyronitrile**

Iodotrimethylsilane (0.6 ml) was added dropwise to a stirred solution of (2S)-2-(BOC-Leu-Leu-NH)-4-methylthiobutyronitrile (0.65 g) in dichloromethane (10 ml) the mixture was stirred at room temperature for 1 hour and then evaporated to dryness. The residue was redissolved in dichloromethane and the solution was treated with methanol (1 ml) and stirred until effervescence ceased. The solution was washed with aqueous sodium bicarbonate solution, dried and evaporated to dryness to give (2S)-2-(H-Leu-Leu-NH)-4-methylthiobutyronitrile as a gum (0.45 g). M/z 357 (MH)⁺.

Method H**Boc-Leu-Leu-NH₂**

A mixture of BOC-Leu-OH (6.93 g), Leu-OMe hydrochloride (5.45 g), 1-hydroxybenzotriazole (4.73 g), 1-dimethylaminopropyl-3-ethylcarbodiimide (6.7 g), *N,N*-dimethylformamide (50 ml) and *N*-methylmorpholine (10 ml) was stirred at room temperature for 18 hours. The mixture was evaporated to dryness and the residue was partitioned between water and ethyl acetate. The organic phase was washed successively with 0.5M hydrochloric acid, 1M sodium hydroxide and brine and then dried and evaporated to dryness. The residue was triturated with a mixture of ether and hexane to give Boc-Leu-Leu-OMe (11 g).

A mixture of a portion of the above ester (4 g), methanol (30 ml) and concentrated aqueous ammonia (50 ml) was stirred at room temperature for 72 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to dryness to give Boc-Leu-Leu-NH₂ (3.3 g). M/z 344.5 (MH)⁺.

Method I**(2S)-2-[(N-phenylacetyl-N-methyl-Leu)-Leu-Met-NH₂]**

Phenylacetyl chloride (0.57 g) was added, dropwise to a stirred, ice cooled solution of *N*-methyl-Leu (0.53 g) in 2M sodium hydroxide (4 ml) and the mixture was stirred at ambient temperature for 3 hours. The mixture was washed with ether and the aqueous phase was acidified with 2M hydrochloric acid and the precipitate collected to give *N*-phenylacetyl-*N*-methyl-Leu-OH (0.33 g). Mp 146-147°C; m/z 264 (MH)⁺.

This was then coupled with H-Leu-Met-NH₂ according to method C to give (2S)-2-[(*N*-phenylacetyl-*N*-methyl-Leu)-Leu-Met-NH₂]. M/z 507 (MH)⁺.

Method I1

(2S)-2-[(N-benzoyl-N-methyl-Leu)-Leu-Met-NH₂ [m/z 493 (MH)⁺] was also obtained by the process described in Method H.

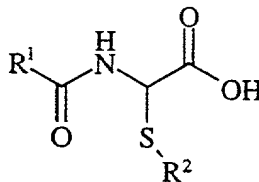
Method J5 **2-benzyloxycarbonylamino-2-phenylthioacetic acid**

A mixture of benzyl carbamate (15.1 g), ether (100ml) and glyoxylic acid monohydrate (10.1 g) was stirred at room temperature for 16 hours. The thick suspension was filtered and the residue was washed with a mixture of ether and hexane to give 2-benzyloxycarbonylamino glycollic acid (17 g), which was used without further purification.

10 A mixture of 2-benzyloxycarbonylamino glycollic acid (2.25 g), 1,2-dichloroethane (50ml) and thiophenol (1.65 g) was stirred at reflux for 2 hours then cooled to room temperature. The mixture was extracted twice with aqueous sodium hydrogen carbonate and the combined extracts were washed with ether then acidified with 2M hydrochloric acid. The mixture was extracted with ether and the extract was dried and evaporated to dryness to give
15 2-benzyloxycarbonylamino-2-phenylthioacetic acid as a white solid (2.45 g). M/z 318 (MH)⁺.

Method J 1 - 4

Following the method outlined in Method J and using the appropriate amide instead of benzyl carbamate in the first stage and the appropriate thiol in the second stage there was prepared:



20

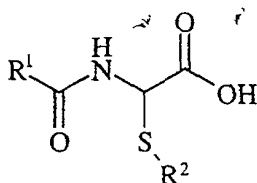
| Method | R ¹ | R ² | MH ⁺ |
|--------|-----------------------------|----------------|-----------------|
| J1 | benzyloxy | 2-propyl | 322 |
| J2 | 2,4,6-trichlorophenoxyethyl | phenyl | 420 |
| J3 | 2,4-dichlorophenyl | phenyl | 356 |
| J4 | benzyloxy | m-tolyl | 332 |

Method K**2-phenylacetamido-2-phenylthioacetic acid**

A mixture of phenylacetamide (2.7 g), glyoxylic acid monohydrate (2.02 g), 1,2-dichloroethane (100 ml), thiophenol (3.3 g) and 2-naphthalenesulphonic acid (100 mg) was stirred at reflux for 16 hours. The mixture was cooled and extracted twice with aqueous sodium hydrogen carbonate and the combined extracts were washed with ether, acidified with 2M hydrochloric acid and extracted with ether. The ether extract was dried and evaporated to dryness to give 2-phenylacetamido-2-phenylthioacetic acid. M/z 302 (MH^+).

Method K 1 - 4

Following the method outlined in Method K and using the appropriate starting materials there was prepared:



| Method | R ¹ | R ² | MH ⁺ |
|--------|-----------------------|----------------|-----------------|
| K1 | naphth-2-yl | phenyl | 338 |
| K2 | naphth-2-yl | naphth-1-yl | 388 |
| K3 | naphth-2-yl | naphth-2-yl | 388 |
| K4 | phenylsulphonylmethyl | phenyl | 366 |

Method L**2-[2-benzyloxycarbonylamino-2-(hydroxy)acetamido]-2-(2-thienyl)-acetonitrile**

A mixture of 2-benzyloxycarbonylamino glycollic acid (1.125 g), 2-aminoacetonitrile hydrochloride (0.7 g), hydroxybenzotriazole (0.75 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.05 g) and 4-methylmorpholine (3 ml) in *N,N*-dimethylformamide (20 ml) was stirred at ambient temperature for 18 hours. The solvent was removed under reduced pressure and the residue was stirred with a mixture of ethyl acetate (100 ml) and 1M Hydrochloric acid and the insoluble solid collected to give 2-[2-benzyloxycarbonylamino-2-(hydroxy)acetamido]-2-(2-thienyl)-acetonitrile. Mp 146-148°C; m/z 264 (MH^+).

Method M**N-(N-Morpholinocarbonyl)-(L)-leucine**

Lithium hydroxide solution (5.9 g in 40 ml water) was added to a solution of N-(N-morpholinocarbonyl)-(L)-leucine methyl ester (Method N) (7.3 g) in THF (40 ml) and the mixture was stirred for 20 hours. The residue obtained on removal of the solvent was suspended in water (150 ml) and washed with ethyl acetate (50 ml). The aqueous layer was acidified to pH 1 with 2M HCl and extracted with ethyl acetate (3x70 ml). The combined ethyl acetate extracts were washed with water (75 ml) and brine (75 ml) and passed through phase-separating paper. Removal of the solvent gave N-(N-morpholinocarbonyl)-(L)-leucine as an oil. NMR: 6.5 (d, 1H), 4.0 (m, 1H), 3.5 (m, 4H), 3.3 (m, 4H), 1.5 (m, 2H), 1.4 (m, 1H), 0.8 (m, 6H).

Method N**N-(N-morpholinocarbonyl)-(L)-leucine methyl ester**

Triethylamine (8.4 ml) was added dropwise to L-leucine methyl ester hydrochloride (5 g) in dichloromethane (50 ml) at 0 °C followed by a solution of 4-morpholine carbonyl chloride (5 g) in dichloromethane (10 ml) and the mixture was stirred at ambient temperature for 20 hours. The reaction mixture was diluted with dichloromethane (100 ml) and washed with water (100 ml). The organic layer was collected and washed with 2M HCl (50 ml), brine (50 ml) and passed through phase-separating paper. Removal of the solvent gave N-(N-morpholinocarbonyl)-(L)-leucine methyl ester as a solid, 7.3 g. NMR: 6.7 (d, 1H), 4.1 (m, 1H), 3.6 (s, 2H), 3.5 (m, 4H), 3.3 (m, 4H), 1.6 (m, 2H), 1.4 (m, 1H), 0.8 (m, 6H); m/z: 259 (M+H)⁺.

Method O**N-[(2-phenylacetyl)amino-2-phenylthio]acetic acid**

This compound was prepared from phenylacetamide, glyoxylic acid and thiophenol following the procedure described in Tetrahedron, 31, 863 1975.

Method O1

Following the method outlined in Method O and using the appropriate starting material there was prepared:

N-[(2-phenylacetyl)amino-2-(4-fluorophenylthio)acetic acid.

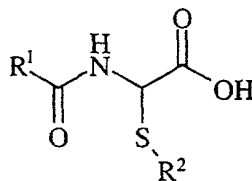
Method P**2-benzyloxycarbonylamino-2-phenylthioacetic acid**

A mixture of benzyl carbamate (15.1 g), ether (100ml) and glyoxylic acid monohydrate (10.1 g) was stirred at room temperature for 16 hours. The thick suspension was
 5 filtered and the residue was washed with a mixture of ether and hexane to give 2-benzyloxycarbonylamino glycollic acid (17 g), which was used without further purification.

A mixture of 2-benzyloxycarbonylamino glycollic acid (2.25 g), 1,2-dichloroethane (50ml) and thiophenol (1.65 g) was stirred at reflux for 2 hours then cooled to room
 10 temperature. The mixture was extracted twice with aqueous sodium hydrogen carbonate and the combined extracts were washed with ether then acidified with 2M hydrochloric acid. The mixture was extracted with ether and the extract was dried and evaporated to dryness to give 2-benzyloxycarbonylamino-2-phenylthioacetic acid as a white solid (2.45 g). M/z 318 (MH)⁺.

Method P 1 - 4

Following the method outlined in Method P and using the appropriate amide instead of
 15 benzyl carbamate in the first stage and the appropriate thiol in the second stage there was prepared:



| Method | R ¹ | R ² | MH ⁺ |
|--------|------------------------------|----------------|-----------------|
| P1 | benzyloxy | 2-propyl | 322 |
| P2 | 2,4,6-trichlorophenoxymethyl | phenyl | 420 |
| P3 | 2,4-dichlorophenyl | phenyl | 356 |
| P4 | benzyloxy | m-tolyl | 332 |

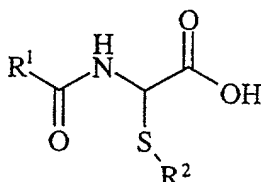
Method Q**2-phenylacetamido-2-phenylthioacetic acid**

20 A mixture of phenylacetamide (2.7 g), glyoxylic acid monohydrate (2.02 g), 1,2-dichloroethane (100 ml), thiophenol (3.3 g) and 2-naphthalenesulphonic acid (100 mg) was stirred at reflux for 16 hours. The mixture was cooled and extracted twice with aqueous sodium hydrogen carbonate and the combined extracts were washed with ether, acidified with

2M hydrochloric acid and extracted with ether. The ether extract was dried and evaporated to dryness to give 2-phenylacetamido-2-phenylthioacetic acid. M/z 302 (MH⁺).

Method Q 1 - 4

- Following the method outlined in Method Q and using the appropriate starting materials there was prepared:



| Method | R ¹ | R ² | MH ⁺ |
|--------|-----------------------|----------------|-----------------|
| Q1 | naphth-2-yl | phenyl | 338 |
| Q2 | naphth-2-yl | naphth-1-yl | 388 |
| Q3 | naphth-2-yl | naphth-2-yl | 388 |
| Q4 | phenylsulphonylmethyl | phenyl | 366 |

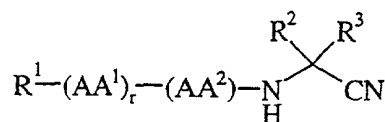
Method R

2-[2-benzyloxycarbonylamino-2-(hydroxy)acetamido]-2-(2-thienyl)-acetonitrile

- A mixture of 2-benzyloxycarbonylamino glycollic acid (1.125 g), 2-aminoacetonitrile hydrochloride (0.7 g), hydroxybenzotriazole (0.75 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.05 g) and 4-methylmorpholine (3 ml) in *N,N*-dimethylformamide (20 ml) was stirred at ambient temperature for 18 hours. The solvent was removed under reduced pressure and the residue was stirred with a mixture of ethyl acetate (100 ml) and 1M Hydrochloric acid and the insoluble solid collected to give 2-[2-benzyloxycarbonylamino-2-(hydroxy)acetamido]-2-(2-thienyl)-acetonitrile. Mp 146-148°C; m/z 264 (MH)⁺.

CLAIMS

1. A compound of formula (I):



5

(I)

wherein

r is 0 or 1;

R^1 is hydrogen, optionally substituted benzyl where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy,

10

trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino,

C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl,

N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto,

C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl,

N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl, or R^1 is a group of formula

15

(II):



(II)

wherein R^5 is C_{1-6} alkyl (optionally substituted with an optionally substituted phenyl, an optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted

20

phenoxy, optionally substituted phenylsulphonyl, optionally substituted C_{3-12} cycloalkyl

or Het), C_{1-6} alkoxy, optionally substituted phenyl, optionally substituted naphthyl,

optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted C_{3-12} cycloalkyl, Het or optionally substituted phenyl C_{1-6} alkoxy; where said optional

substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino,

25

C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl,

N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto,

C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl,
N-(C₁₋₆alkyl)sulphamoyl and N,N-(C₁₋₆alkyl)₂sulphamoyl;

R² is H, C₁₋₆alkyl [optionally substituted with one or more of hydroxy,

C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, R⁴, R⁴C₁₋₆alkylsulphanyl,

5 R⁴C₁₋₆alkylsulphinyl, R⁴C₁₋₆alkylsulphonyl], or R² is C₁₋₆alkoxy [optionally substituted
with one or more of C₂₋₆alkenyl, C₂₋₆alkynyl, R⁴, R⁴C₂₋₆alkenyl, R⁴C₂₋₆alkynyl, Het and
trifluoromethyl], or R² is C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxycarbonyl, carbamoyl,

N-(C₁₋₆alkyl)carbamoyl, N,N-(C₁₋₆alkyl)₂carbamoyl, R⁴, R⁴S, R⁴C₁₋₆alkylsulphanyl,

N-(R⁴C₁₋₆alkyl)carbamoyl, N-(HetC₁₋₆alkyl)carbamoyl, C₁₋₆alkanoylamino,

10 C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl or C₁₋₆alkylsulphonyl; R⁴ is an optionally
substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl ring
containing a maximum of four heteroatoms, said optional substituents being chosen
from one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy,

cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino,

15 N,N-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl,

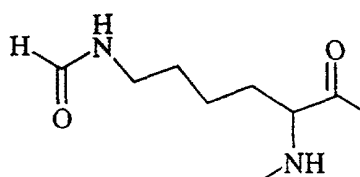
N-(C₁₋₆alkyl)carbamoyl, N,N-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto,

C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl,

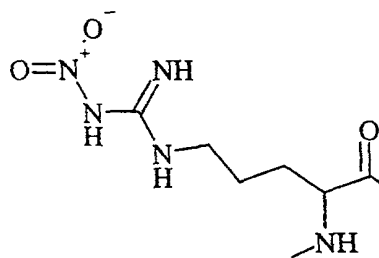
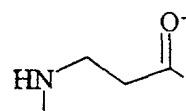
N-(C₁₋₆alkyl)sulphamoyl and N,N-(C₁₋₆alkyl)₂sulphamoyl;

R³ is H or C₁₋₆alkyl;

20 (AA¹) and (AA²) are independently chosen from Ala, Arg, Cys, Gly, His, Ile, Leu, Lys,
Met, Phe, Ser, Thr, Trp, Tyr, Val,

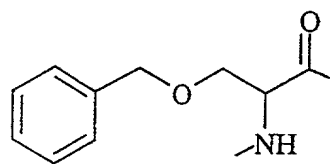


Lys(CHO),

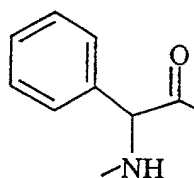
Arg(NO₂),

β-Ala,

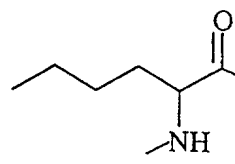
66



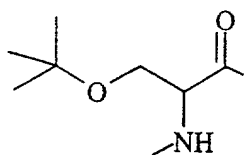
Ser(Bzl),



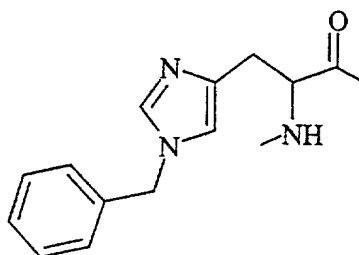
Ph-Gly,



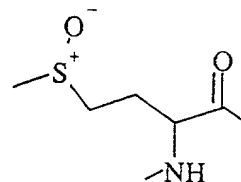
Nle,



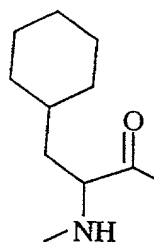
Ser(O<sup>t</sup>Bu),



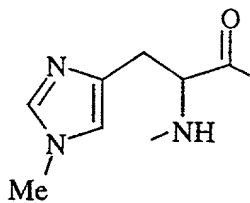
His(Bzl),



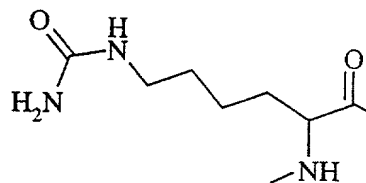
Met(O),



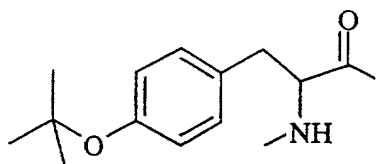
Cha,



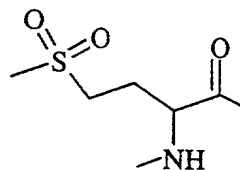
His(Me),



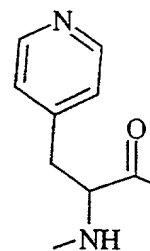
Cit,



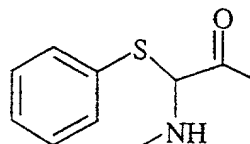
Tyr(<sup>t</sup>Bu),



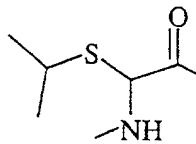
Met(O<sub>2</sub>),



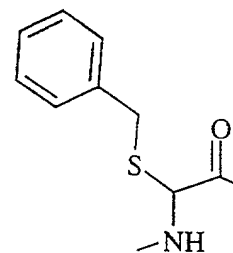
Pyr-Ala



Phe(S),



Leu(S),



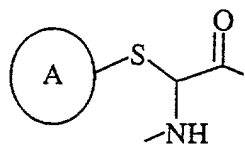
Phe(CH<sub>2</sub>S),

5

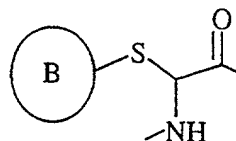
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200510-0151660

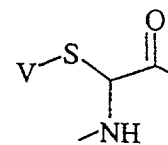
67



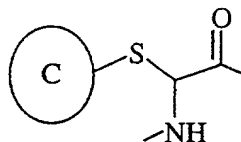
Cy(S)-Gly,



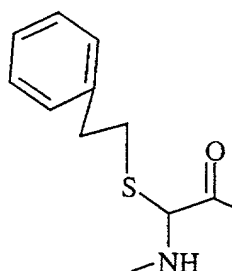
Hetar(S)-Gly,



alk(S)-Gly or



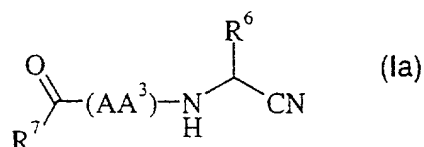
Het(S)-Gly, and

Phe(CH₂CH₂)S;

- 5 wherein Ring A is C₃₋₁₂cycloalkyl; Ring B is a 5 or 6 membered heteroaryl ring; Ring C is Het; V is C₁₋₆alkyl excluding isopropyl; the nitrogen of the amino acid may optionally be alkylated with C₁₋₆alkyl; the phenyl group of Phe(S) and Rings A and B are optionally substituted with one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, 10 *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl or *N,N*-(C₁₋₆alkyl)₂sulphamoyl; the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group; the sulphur moiety in the α-position of the amino acid (AA³) may be optionally oxidised to form an -S(O)₂- or -S(O)- moiety; and 15 Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms; or a pharmaceutically acceptable salt thereof.

20

2. A compound as claimed in claim 1 having the formula (Ia):

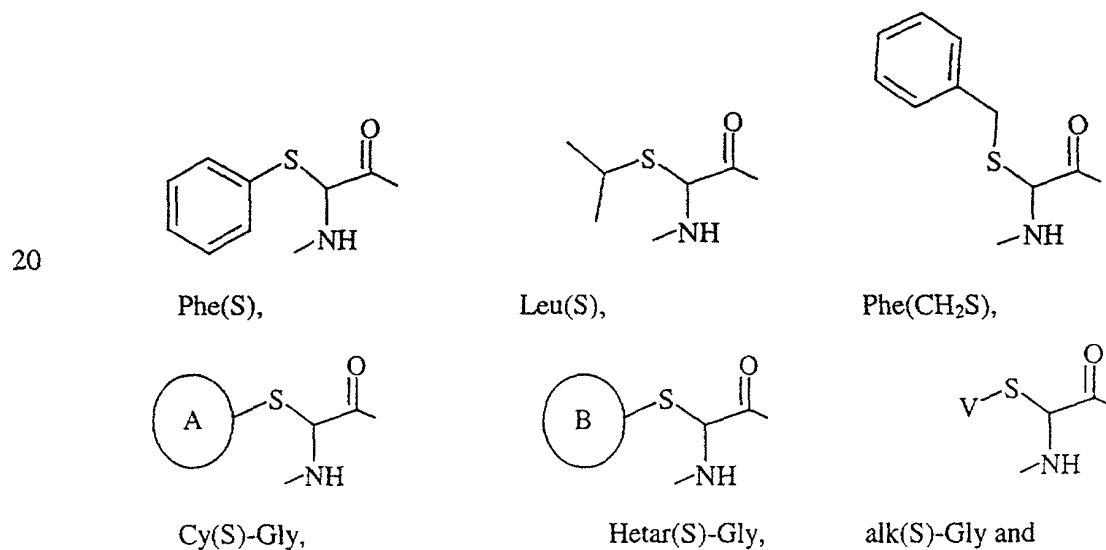


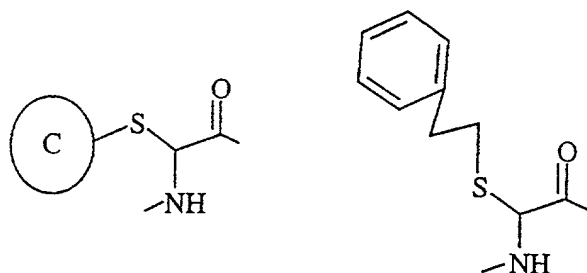
wherein:

R^7 is optionally substituted benzyl, optionally substituted phenoxymethyl, optionally substituted phenylsulphonylmethyl, optionally substituted benzyloxy, optionally substituted naphthyl, optionally substituted phenyl or t-butoxy where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

R^6 is hydrogen, optionally substituted phenyl or optionally substituted 5 or 6 membered heteroaryl ring containing a maximum of four heteroatoms; said optional substituents being chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

(AA^3) is selected from:





Het(S)-Gly, and

Phe(CH₂CH₂)S;

wherein Ring A is C₃₋₁₂cycloalkyl, Ring B is a 5 or 6 membered heteroaryl ring, Ring C is Het, V is C₁₋₆alkyl excluding isopropyl; the nitrogen of the amino acid may optionally be alkylated with C₁₋₆alkyl; the phenyl group of Phe(S) and Rings A and B may be optionally substituted with one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl; the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group; the sulphur moiety in the α -position of the amino acid (AA³) may be optionally oxidised to form an -S(O)₂- or -S(O)- moiety; and

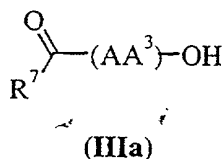
Het is a fully saturated monocyclic 5 - 8 membered heterocyclic ring, with up to 4 ring heteroatoms;
or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in claim 2 wherein R⁶ is hydrogen, optionally substituted phenyl or a 5 membered heteroaryl ring containing a maximum of four heteroatoms.
4. A compound as claimed in claim 2 or 3 wherein R⁷ is benzyl (optionally substituted with halo (such as chloro)), α -(C₁₋₄ alkyl)-benzyl (optionally substituted with halo (such as chloro)), α,α -di(C₁₋₄ alkyl)-benzyl (optionally substituted with halo (such as chloro)), optionally substituted phenoxyethyl, phenylsulphonylmethyl, benzyloxy, naphthyl or optionally substituted phenyl where said optional substituents are chosen from one or more halo.

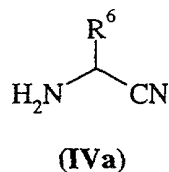
5. A compound as claimed in claim 2, 3 or 4 wherein (AA³) is Leu(S), Phe(S) optionally substituted with C₁₋₆alkyl or halo and wherein the phenyl group of Phe(S) may be fused to another phenyl group to form a naphthyl group or the sulphur moiety in the α-position of the amino acid (AA) may be optionally oxidised to form an -S(O)₂- or Phe(CH₂S).

6. A process for preparing a compound of formula (Ia) as claimed in claim 2 comprising:

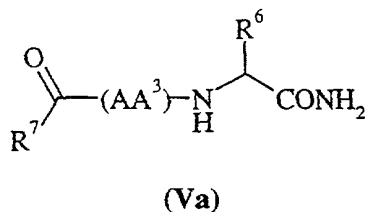
a) coupling an acid of formula (IIIa):



or a reactive derivative thereof, with an amine of formula (IVa):

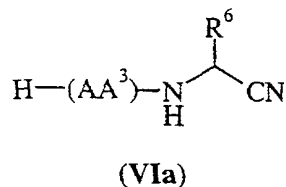


b) dehydrating a compound of formula (Va):

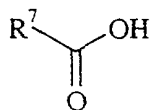


under standard conditions; or,

c) reacting an amine of formula (VIa):



with an acid of formula (VIIa):

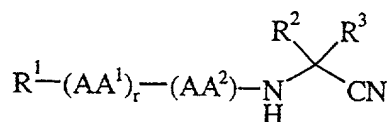


(VIIa)

or a reactive derivative thereof;

wherein R^6 , R^7 and AA^3 are as defined in claim 2.

- 5 7. A compound of formula (I):



(I)

wherein:

r is 0 or 1;

- 10 R^1 is optionally substituted benzyl where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, 15 C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, sulphamoyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl or R^1 is a group of formula (II):



(II)

- 20 wherein R^5 is C_{1-6} alkyl (optionally substituted with an optionally substituted phenyl, an optionally substituted 5 or 6 membered heteroaryl ring, optionally substituted phenoxy or optionally substituted phenylsulphonyl), C_{1-6} alkoxy, optionally substituted phenyl, optionally substituted naphthyl, optionally substituted phenyl C_{1-6} alkoxy where said optional substituents are chosen from one or more of C_{1-6} alkyl, halo, 25 trifluoromethyl, hydroxy, trifluoromethoxy, cyano, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, amino, C_{1-6} alkylamino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, nitro, carboxy, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkoxycarbonyl, mercapto, C_{1-6} alkylsulphanyl, C_{1-6} alkylsulphinyl,

C₁₋₆alkylsulphonyl, sulphamoyl, *N*-(C₁₋₆alkyl)sulphamoyl and
N,N-(C₁₋₆alkyl)₂sulphamoyl;

R² is H, C₁₋₆alkyl [optionally substituted with one or more of hydroxy,

C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, **R**⁴, **R**⁴C₁₋₆alkylsulphanyl,

5 **R**⁴C₁₋₆alkylsulphinyl, **R**⁴C₁₋₆alkylsulphonyl], or **R**² is C₁₋₆alkoxy [optionally substituted
 with one or more of C₂₋₆alkenyl, C₂₋₆alkynyl, **R**⁴, **R**⁴C₂₋₆alkenyl, **R**⁴C₂₋₆alkynyl, Het and
 trifluoromethyl], or **R**² is C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxycarbonyl, carbamoyl,
N-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, **R**⁴, **R**⁴S, **R**⁴C₁₋₆alkylsulphanyl,
N-(**R**⁴C₁₋₆alkyl)carbamoyl, *N*-(HetC₁₋₆alkyl)carbamoyl, C₁₋₆alkanoylamino,

10 C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl wherein **R**⁴ is an optionally
 substituted phenyl, or an optionally substituted 5 or 6 membered heteroaryl ring
 containing a maximum of four heteroatoms said optional substituents being chosen
 from one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy,
 cyano, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino,

15 *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl,
N-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto,
 C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl,
N-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl;

R³ is H or C₁₋₆alkyl; and

20 (**AA**¹) and (**AA**²) are independently chosen from Ala, Arg, Cys, Gly, His, Ile, Leu, Lys,
 Met, Phe, Ser, Thr, Trp, Tyr, Val, Lys(CHO), Arg(NO₂), β-Ala, Ser(Bzl), Ph-Gly, Nle,
 Ser(O^tBu), His(Bzl), Met(O), Cha, His(Me), Cit, Tyr(^tBu), Met(O₂), Pyr-Ala, Phe(S),
 Leu(S) or Phe(CH₂S); wherein the nitrogen of the amino acid may optionally be

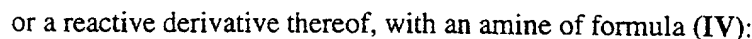
25 alkylated with C₁₋₆alkyl and the phenyl group of Phe(S) may be optionally substituted
 with one or more of C₁₋₆alkyl, halo, trifluoromethyl, hydroxy, trifluoromethoxy, cyano,
 C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, amino, C₁₋₆alkylamino,

N,N-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, nitro, carboxy, carbamoyl,
N-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl, mercapto,
 C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphinyl, C₁₋₆alkylsulphonyl, sulphamoyl,

30 *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl or the phenyl group may be
 fused to another phenyl group to form a naphthyl group; or a pharmaceutically
 acceptable salt thereof.

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- 10



(IV)

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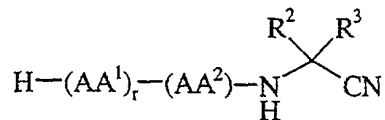
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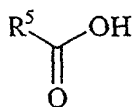


d) for compounds of formula (I) where R^1 is a group of formula (II), reacting an amine of formula (VIII):



(VIII)

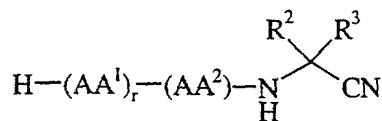
5 with an acid of formula (IX):



(IX)

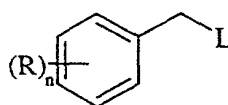
or a reactive derivative thereof as defined hereinbefore; or

10 e) for compounds of formula (I) where R^1 is optionally substituted benzyl, reacting an amine of formula (X):



(X)

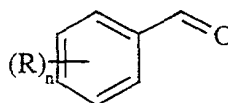
i) with a compound of formula (XI):



(XI)

15 where $(R)_n$ are optional substituents as defined above and L is a displaceable group; or

ii) with an aldehyde of formula (XII):

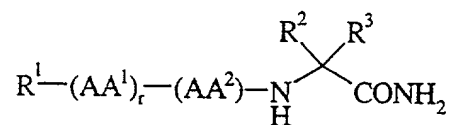


(XII)

20 where $(R)_n$ are optional substituents as defined above and L is a displaceable group;

wherein R^1 , R^2 , R^3 , AA^1 , AA^2 and r are as defined in claim 1.

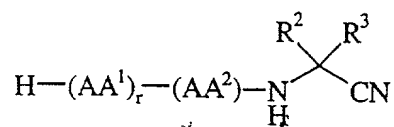
11. A compound of formula (V):



(V)

- 5 wherein R^1 , R^2 , R^3 , AA^1 , AA^2 and r are as defined in claim 1.

12. A compound of formula (VIII):



(VIII)

- 10 wherein R^1 , R^2 , R^3 , AA^1 , AA^2 and r are as defined in claim 1.

13. A pharmaceutical composition comprising a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, 2, 8 or 9 and a pharmaceutically acceptable diluent or carrier.

15

14. A compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, 2, 8 or 9 for use as a medicament

15. The use of a compound of formula (I) or (Ia) as claimed in claim 1, 2, 8 or 9, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal.

20

16. The use of a compound of formula (I) or (Ia) as claimed in claim 1, 2, 8 or 9, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease in a warm blooded animal.

25

17. A method of treating a Cathepsin L or Cathepsin S mediated disease state in mammals which comprises administering to a mammal in need of such treatment an effective

amount of a compound of formula (I) or (Ia) as claimed in claim 1, 2, 8 or 9, or a pharmaceutically acceptable salt thereof.

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COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled ,

DI- AND TRIPEPTIDE NITRILE DERIVATIVES AS INHIBITORS OF CATHEPSIN L AND CATHEPSIN S

the specification of which

- ☐ is attached hereto.
☐ was filed on as Application Serial No. and was amended on .
 X was described and claimed in PCT International Application No. PCT/GB00/00529 filed on 16th February 2000 and as amended under PCT Article 19 on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

| COUNTRY | APPLICATION NO. | FILING DATE | PRIORITY CLAIMED |
|---------------|-----------------|------------------|-----------------------------------|
| Great Britain | 9903853.1 | 20 February 1999 | X Yes <input type="checkbox"/> No |
| Great Britain | 9916099.6 | 10 July 1999 | X Yes <input type="checkbox"/> No |
| Great Britain | 9917171.2 | 23 July 1999 | X Yes <input type="checkbox"/> No |

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

| U.S. SERIAL NO | FILING DATE | STATUS |
|----------------|-------------|---|
| | | <input type="checkbox"/> Pending <input type="checkbox"/> Issued <input type="checkbox"/> Abandoned |

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Janis K. Fraser, Reg. No. 34,819; Celia H. Leber,

COMBINED DECLARATION AND POWER OF ATTORNEY CONTINUED

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Janis K. Fraser, Reg. No. 34,819; Celia H. Leber, Reg. No. 33,524; John W. Freeman, Reg. No. 29,066; John F. Hayden, Reg. No. 37,640; John T. Li, Reg. No. 44,210; J. Peter Fasse, Reg. No. 32,983. (6)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

1-00
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